CUK- H04629-26-P024954

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Published by the
BMJ Publishing Group,
Tavistock Square, London
WC1H 9JR and printed
in England by
The Devonshire Press Ltd,
Torquay.

Second class postage paid,
Rahway NJ. Postmaster:
send address changes to:
Archives of Disease in
Childhood, c/o Mercury
Airfreight International
Ltd Inc, 2323 Randolph
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ISSN 0003-9888

NOTES TO CONTRIBUTORS Papers for publication should be sent to the Editors, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR and should be prepared in accordance with the 'Instructions to authors' published in the January and June issues of the journal. Copies of these instructions may be obtained from the editorial office on receipt of a stamped addressed envelope.

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Published by the BMJ Publishing Group, Tavistock Square, London WC1H 9JR and printed in England by The Devonshire Press Ltd, Torquay.

Second class postage paid, Rahway NJ. Postmaster send address changes to Archives of Disease in Childhood, c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NH 07001, USA

ISSN 0003-9888

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ISSN 0003-9888

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ISSN 0003-9888

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The Devonshire Press Ltd,
Torquay.

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send address changes to.
Archives of Disease in
Childhood, c/o Mercury
Airfreight International
Ltd Inc, 2323 Randolph
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ISSN 0003-9338

Archives of Disease in Childhood 1992; 67: 473–474

Acc 28 7/93

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CHILDHOOD

The Journal of the British Paediatric Association

Annotation

Neonatal BCG immunisation

Since its introduction in 1921 the efficacy of bacille Calmette-Guérin (BCG) has been extensively debated, yet it remains one of the most widely used of all vaccines today. BCG is compulsory in 64 countries and is officially recommended in a further 118.[1] Schedules differ widely, a testimony to the lack of consensus regarding timing of immunisation. There is growing evidence that neonatal BCG immunisation significantly reduces the risk of clinical tuberculosis.

The controversy

In 10 randomised controlled trials conducted throughout the world since the 1930s, the protective efficacy of BCG vaccination (percentage reduction in risk attributable to vaccination) ranged from 0–80%.[2] The largest and most widely publicised trial from southern India, which reported no protection, only investigated sputum positive disease and did not include neonates.[3] Only two out of these 10 trials evaluated neonatal BCG vaccination. Both were performed in North America and vaccine efficacy was estimated to be 75–80%.[4 5]

An alternative form of assessing the vaccine is the case-control study in which identified cases of infection have been matched with up to four controls. Those studies which have specifically addressed neonatal BCG vaccination have reported protection rates greater than 80%.[6 7]

Several factors may explain the widely divergent results of the major trials. These include vaccine potency, study design, age at vaccination, regional differences in *Mycobacterium tuberculosis* strains, nutritional or genetic differences in the trial population, and interaction of vaccines with different mycobacteria which may reduce vaccine efficacy.[1] The answer defies a simple explanation and it is probable that multiple variables are operational.

Although tuberculin sensitivity is the clinical marker of an immunological response to BCG, a positive tuberculin test does not always imply protection to the disease.[8] In a Birmingham study, which demonstrated a protective effect of BCG, there were 108 children with tuberculosis of whom 62 had received the vaccine. Of these 36 had postvaccination testing (three months later) and 31 were found to be tuberculin positive.[9] Approximately 90% of children have been found to be tuberculin positive four to five years after neonatal BCG.[10 11]

BCG immunisation and tuberculous meningitis

Tuberculosis of the central nervous system continues to be the most devastating form of childhood tuberculosis. Major neurological sequelae follow in up to 70% of cases,[12] with reported mortality rates of 20%.[13] Several case-control studies have reported vaccine efficacy of 85–100% against tuberculous meningitis.[6 7 14] There is evidence that the effect of BCG vaccination is to limit the multiplication and dissemination of the tubercle bacillus.[15] Immunisation does not prevent the establishment of infection in someone exposed to disease. This may explain the higher protection afforded against tuberculous meningitis and other disseminated forms of tuberculosis.

Neonatal BCG immunisation and immunodeficiency syndromes including HIV infection

Several cases have been reported of disseminated BCG in adults with symptomatic HIV infection at the time of immunisation.[16] Disseminated disease has been described after BCG in an infant born to a mother with AIDS related complex.[17] In a prospective study in the Congo the frequency of BCG lymphadenitis in a group of HIV infected children was not significantly different from a group of uninfected children after neonatal BCG.[18] Disseminated forms of disease were not seen. It is not known whether BCG is protective in children who are HIV positive. The World Health Organisation has recommended that neonatal BCG should be given in areas where there is a high prevalence of both tuberculosis and HIV infection.[19] But BCG is not recommended for HIV infected children (asymptomatic or symptomatic) in areas of low tuberculosis endemicity. As yet there is no indication to check HIV status in those infants from the high risk groups before administering BCG. The risk of disseminated BCG infection among babies with severe congenital immunodeficiency is unknown. Disseminated BCG was seen in 1/300 000 newborn infants given BCG routinely in Chile; those infants affected were thought to have congenital immunodeficiency.[20] In a British population the incidence of severe combined immunodeficiency is thought to be 1/60 000.

Complications of neonatal BCG

Ulceration at the site of inoculation and osteitis are said to be more common in the newborn. An incidence of BCG osteitis of 29/100 000 prompted Sweden to abandon their neonatal BCG programme in 1975.[21] This particularly high incidence may have been related to the strain of vaccine used.

Tuberculosis in the UK

There were 5432 cases of tuberculosis notified to the Office of Population and Census and Surveys in 1989.[22] Ten per cent of cases occurred in children. Tuberculous meningitis accounted for less than 1% of the total cases but 30% of these occurred in children. In a survey in 1983 of all notifications of tuberculosis in children the highest rates occurred in children of Indian subcontinent ethnic origin: 32/100 000 for the Indian and 52/100 000 for the Pakistani and Bangladeshi groups.[23] The rate for white children was 2·4/100 000. Nevertheless white children accounted for 48% of the total number of cases. Altogether 75% of cases of tuberculous meningitis occurred in children under 5 years and were thus in the age group that could have been protected by neonatal BCG vaccination.

Current practice in the UK

The Department of Health[24] and the British Paediatric Association[25] recommend a selective policy of neonatal BCG vaccination. They advise that the following groups should receive the vaccine at birth: (i) babies of Asian and other immigrant families with high tuberculosis rates, (ii) infants who reside in or travel to areas where the risk of contracting tuberculosis is thought to be high, (iii) those in contact with active respiratory tuberculosis, and (iv) infants with a family history of tuberculosis in the preceding five years. In a recent yet unpublished survey carried out by the Public Health Laboratory Service (PHLS), Communicable Disease Surveillance Centre, 31 out of 174 district health authorities in England and Wales did not offer BCG immunistaion to the newborn (John Watson, PHLS, personal communication). In addition to the high risk groups referred to above there may be areas where other children are at risk. The rate of tuberculosis in white inner city Leeds children at 5·5/100 000 was similar to that of children whose parents originated from the Indian subcontinent (5·2/100 000).[26]

Conclusion

Neonatal BCG offers almost complete protection to meningitis and other disseminated forms of tuberculosis in childhood. It is less effective against respiratory disease protecting some 65% of children exposed to infection.[6 7] Although the incidence of tuberculosis in the UK declined in the early 1980s there has been a recent increase, possibly related to the HIV epidemic, but increases in notifications have been seen in districts with high proportions of residents of Indian subcontinent ethnic origin.[27] Paediatricians should ensure that children at high risk of tuberculosis are protected from this disease.

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ANTONIA CLARKE
PETER RUDD

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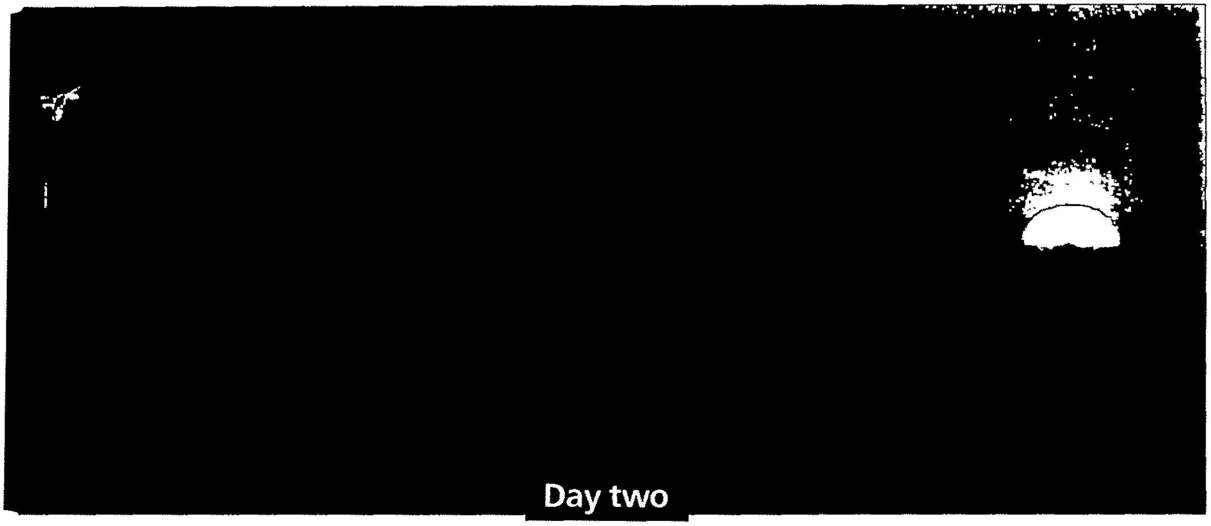

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The
HEALTH
of the
NATION
THE BMJ VIEW

Edited by Richard Smith, Editor of the BMJ

"...a strategy imposed by the government which takes no heed of the views of those who will have to implement it...is valueless". So writes William Waldegrave, Secretary of State for Health, in his introduction to *The Health of the Nation*, the government's consultative document that sets out a strategy for improving the health of the English. Taking Mr Waldegrave at his word on wanting to listen to everybody, the *BMJ* commissioned a series of articles that explain the views of some of those most concerned. Contributors discuss each of the 16 key areas defined in the strategy and suggest other subjects that might qualify as key areas. One article, from the Radical Statistics Health Group, is strongly critical of the strategy; others are critical of various aspects of it, but almost all of the contributors support the idea of setting targets for improving health. Originally published in the *BMJ*, this collection of articles is an important contribution to the debate on how to achieve health for the nation. Furthermore, the articles will be useful beyond the borders of England because most developed countries are now setting strategies to improve health.

Published 27 November 1991
UK £9.95; Abroad £12.00 (BMA members £8.95 or £11.00) including postage, by air abroad.

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ORIGINAL ARTICLES

Immunogenicity and safety of PRP-T conjugate vaccine given according to the British accelerated immunisation schedule

R Booy, S A Taylor, S R M Dobson, D Isaacs, G Sleight, S Aitken, H Griffiths, H Chapel, R T Mayon-White, J A Macfarlane, E R Moxon

Abstract

The immunogenicity and safety of a new *Haemophilus influenzae* type b conjugate vaccine, PRP-T, was studied in 107 infants from the Oxford district. The vaccine was given concurrently with diphtheria, pertussis, tetanus, and polio vaccines at 2, 3, and 4 months of age. Symptoms after immunisation were recorded by a parent. Sera were obtained before the first immunisation and at 5 months of age and the antibodies were measured by both radioimmunoassay and enzyme linked immunosorbent assay (ELISA). No serious adverse reactions were observed and there was no increase in the incidence of expected minor side effects. By radioimmunoassay, the geometric mean titre of serum anticapsular antibody increased from 0·09 µg/ml before immunisation to 5·01 µg/ml after three immunisations. Ninety eight per cent of children had antibody concentrations consistent with protection (≥0·15 µg/ml). IgG antibody concentrations measured by ELISA correlated well with total antibody concentrations measured by radioimmunoassay (r=0·864). These results provide encouragement that routine immunisation against *H influenzae* type b at 2, 3, and 4 months of age, could prevent most cases of disease in children in the UK.

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Accepted 11 December 1991

Haemophilus influenzae type b is a major cause of serious bacterial infection in early childhood, during which it is the most common cause of meningitis, epiglottitis, cellulitis, and septic arthritis.[1] Epidemiological surveillance in the Oxford region of the UK over the past seven years has underlined the continuing importance of *H influenzae* type b infection.[2] The cumulative risk of infection for children by their fifth birthday is one in 600.

Serum antibodies to the polyribosylribitol phosphate (PRP) capsule of *H influenzae* type b are protective.[3] However, purified polysaccharide vaccine (composed of PRP) is poorly immunogenic in children less than 2 years old,[4] the age group in which most infections occur. This age related susceptibility, first documented in the 1930s, was found to correlate with absent or low concentrations of serum antibodies to PRP, a finding that is typical of infants in their first and second years.[5] Enhancement of the immunoprotective response to polysaccharide antigen is possible through its covalent linkage (conjugation) to a carrier protein,[6] which results in T cell dependency and a boostable response, thereby offering the potential of antibody responses that would protect young infants. Four conjugate vaccines against *H influenzae* type b have been developed, conjugates of PRP respectively to diphtheria toxoid (PRP-D), tetanus toxoid (PRP-T), a diphtheria toxin mutant (HbOC), and an outer membrane protein of meningococcus (PRP-OMP).

Immunogenicity studies comparing these conjugate vaccines given according to current Finnish and American primary immunisation schedules (Finnish: 4 and 6 months of age; USA 2, 4, and 6 months of age), suggest that PRP-T is at least as immunogenic as other conjugate vaccines and it has been shown to result in a greater antibody response after one or two injections than PRP-D or HbOC.[7, 8] Also, the booster response to PRP-T is significantly greater than that seen with PRP-OMP.[8] Thus PRP-T appears an acceptable candidate for inclusion in the British schedule of immunisation at 2, 3, and 4 months of age.

Routine immunisation against *H influenzae* type b of infants under 6 months of age has become part of the routine primary schedule in the USA and several European countries.[9] The Department of Health has indicated that the UK will implement routine immunisation in October 1992. It has been shown previously that the conjugate vaccine HbOC is highly immunogenic in UK infants using the primary schedule of 3, 5, and 9 months,[10] but in May 1990 the primary schedule in the UK was altered to 2, 3, and 4 months of age. The purpose of this study was to determine the safety and immunogenicity of the conjugate vaccine PRP-T when given concurrently with diphtheria, pertussis, tetanus, and polio vaccines and according to the accelerated schedule of primary immunisation at 2, 3, and 4 months of age. Antibody concentrations to PRP were measured by both radioimmunoassay and enzyme linked immunosorbent asasy (ELISA) as part of the validation of the ELISA used.

Patients and methods

One hundred and seven Oxfordshire infants were recruited over a two month period. Parents were approached on the second or subsequent days after birth with information about the study. Written consent was not requested until the child was at least 6 weeks of age. Seventy five per cent of those invited agreed to take part. Infants were randomised to receive one of three batches of PRP-T (Pasteur Merieux Serum et Vaccins; batch numbers S2141, S2181, S2189). PRP-T is a freeze dried lyophilised conjugate vaccine which is reconstituted with 0·5 ml sodium chloride 0·4%. Immunisations took place in the family home at 2, 3, and 4 months of age. *H influenzae* type b vaccine was given by intramuscular injection in the right thigh and, at the same visit, diphtheria, pertussis, and tetanus vaccine (Wellcome) was given in the left thigh. Oral polio vaccine was also administered. Blood for serology was obtained at the first visit and again one month after completing the primary series. Blood samples were separated on the day of venepuncture and serum stored in 0·5 ml aliquots at −20°C until required.

Parents were given a form to document any symptoms in the three days after each immunisation. They recorded axillary temperatures daily and at any other time if the infant felt hot. The size of local redness or swelling was measured with a calliper. Parents were taught how to use a thermometer and the calliper and were telephoned within one to three days of immunisation to check on progress. They were not told the side on which a particular injection was given, so infants acted as their own control for local reactions.

Total anti-PRP antibodies were measured using Farr type radioimmunoassay[11] by Dr H Kayhty and L Saarinen at the National Public Health Institute in Finland with the standard reference serum from the Food and Drug Administration, USA (72 µg per ml).

IgG antibodies to PRP were measured in Oxford by an ELISA using a modification of the method described by Kumararatne *et al.*[12] All incubations were at room temperature for one hour unless otherwise stated and were followed by four washes with phosphate buffered saline plus 0·05% Tween 20 (PBS-T). PRP (provided by Pasteur-Merieux Serum et Vaccins, France) was covalently bound to poly-L-lysine[13] and diluted in 0·05 M carbonate buffer (pH 9·6) to approximately 1 µg/ml. This solution was added to flat bottomed microtitre plates (Immulon 1, Dynatech) using 100 µl per well and incubated overnight at 4°C. Aliquots of 100 µl of test or standard sera diluted in PBS-T were added to each well. After incubation, the wells were exposed to mouse antihuman IgG diluted in PBS-T, followed by peroxidase conjugated sheep antimouse IgG diluted in PBS-T and finally to substrate solution (0·4 mg/ml o-phenylenediamine dihydrochloride in 0·15 M citrate phosphate buffer, pH 5 with 1 µl hydrogen peroxide per 5 ml substrate solution). The colour was allowed to develop in the dark and the reaction was stopped after 30 minutes by the addition of 25 µl 10% sulphuric acid. The optical density was measured at 492 nm using a Multiscan ELISA reader. A log linear standard curve was plotted with antibody concentration against optical density, from which the antibody concentration of the test samples could be calculated. The lower limit of sensitivity of the assay was 0·16 µg/ml. A standard reference serum was obtained from Dr H Kayhty in Finland. Both the Oxford and Finnish laboratories take part in the European quality control scheme for standardisation of measurement of antibodies to *H influenzae* type b.

Approval for the trial was granted by the central Oxford research ethics committee.

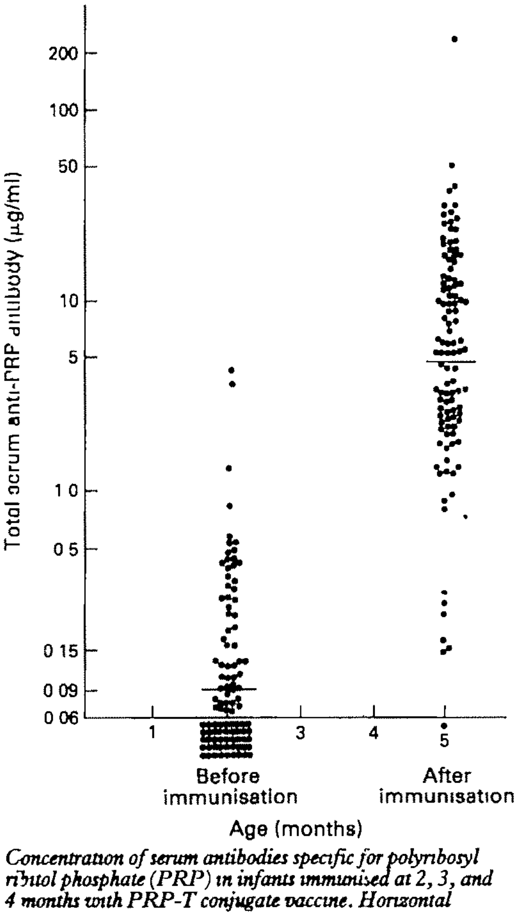
Statistical analyses were performed using Epi Info version 5. Analysis of variance was used for the comparison of response to vaccine batches and the Kruskal-Wallis test was used for comparisons of non-parametric data.

Results

All 107 infants tolerated immunisation for *H influenzae* type b well and none failed to complete the study. A comparison of side effects can be seen in table 1. Local reactions

Table 1 Number of infants with side effects after immunisation with H influenzae type b conjugate and diphtheria, pertussis, and tetanus vaccines (n=107)

	Immunisation dose		
	First	*Second*	*Third*
Redness or swelling at:			
Site of PRP-T injection	1	4	2
Site of diphtheria, pertussis, and tetanus injection	16	27	29
General reactions:			
Axillary temperature ≥38°C	6	5	6
Irritability >4 hours total	30	20	29
Inconsolable crying (maximum observed was six hours)	2	3	2



Concentration of serum antibodies specific for polyribosyl ribitol phosphate (PRP) in infants immunised at 2, 3, and 4 months with PRP-T conjugate vaccine. Horizontal bars=geometric mean titres (Results less than the lower limit of sensitivity of the assay were assigned a value of 0·03 for calculation of the geometric mean titre.)

(redness or swelling) were less common with PRP-T than with the diphtheria, pertussis, and tetanus vaccine. Systemic reaction rates were similar after each of the three primary immunisations. Two children had inconsolable crying and extensive local reactions to their first diphtheria, pertussis, and tetanus immunisations so pertussis was subsequently withheld. Their second and third immunisations were well tolerated.

Sufficient blood for analysis was obtained from 101 infants before immunisation and 107 infants after immunisation. The PRP-T vaccine was immunogenic, such that after the three dose course, 105 of the 107 children (98%) had antibody concentrations consistent with protection (≥0·15 μg/ml) as determined by radioimmunoassays. Ninety seven children (91%) had an antibody concentration of more than 1 μg/ml. The geometric mean titre of antibody to PRP rose from 0·09 μg/ml at 8 weeks of age to 5·01 μg/ml at 20 weeks of age (figure).

IgG antibody concentrations measured by ELISA showed a good correlation with total antibody concentrations measured by radioimmunoassay (r=0·864). By ELISA, only one child had a postimmunisation antibody concentration of <0·16 μg/ml and 90% of children had an antibody concentration of >1·0 μg/ml after immunisation.

All three batches of PRP-T vaccine elicited similar responses; analysis of variance showed no significant difference between batches in either the preimmunisation or postimmunisation antibody concentrations (p>0·1, table 2).

Among infants who had postimmunisation concentrations of ≥0·15 μg/ml by radioimmunoassay there were four who had less than fourfold rises in antibody concentrations. These all had anti-PRP antibody concentrations of >0·15 μg/ml before immunisation. The effect of maternally derived anti-PRP antibodies on the serum antibody response to PRP-T was therefore evaluated. This was done by dividing infants into two groups according to preimmunisation antibody concentrations using 0·15 μg/ml to divide the high and low antibody groups; postimmunisation antibody concentrations of the two groups were then compared. There was no significant differences (table 3; Kruskal-Wallis test, p>0·1). The antibody concentrations in the two infants not achieving 0·15 μg/ml postimmunisation was also <0·15 μg/ml before immunisation.

Table 2 Geometric mean anti-PRP antibody titres for three batches of PRP-T, before and after immunisation (μg/ml)

Vaccine batch	*Geometric mean titre*	
	Before	*After*
S2141	0·08	4·61
S2181	0·10	4·12
S2189	0·09	6·44
Overall	0·09	5·01

Table 3 Effect of maternally derived antibody on anti-PRP antibody responses evoked by PRP-T given at 2, 3, and 4 months of age in 101 infants. (There was insufficient serum in six infants for analysis of antibody titres before immunisation)

	Low group	*High group*
Maternally derived anti-PRP antibody concentration (μg/ml) before immunisation	<0·15	≥0·15
No of infants	30	71
Geometric mean anti-PRP antibody titre (μg/ml):		
Before immunisation	0·05	0·40
After immunisation	4·66	5·81

Discussion

This study demonstrates that an accelerated three dose series of PRP-T immunisation, which is completed by 4 months of age, is both immunogenic and well tolerated. Local reactions were uncommon and the rate of general reactions was similar to that previously reported for UK children immunised with diphtheria, pertussis, tetanus vaccine alone or diphtheria, pertussis, tetanus and *H influenzae* type b conjugate vaccine according to the 3, 5, and 9 months schedule.[10,14]

There was a good correlation between antibody concentrations measured by radioimmunoassay and by ELISA, the latter measuring only IgG antibodies. Similar findings have been reported previously, with total antibodies measured by both methods.[15] These results show that ELISA can be used as an alternative to the classical radioimmunoassay for reliable measurement of PRP antibodies. The ELISA has other potentially valuable uses such as measurement of isotype specific antibodies and IgG subclass antibodies.

An inhibitory effect by placentally transferred antibodies was suggested in a previous immunogenicity study of a prototype PRP-tetanus toxoid conjugate vaccine.[16] In contradiction, our study demonstrated that the immune response to PRP-T was not significantly affected by preimmunisation anti-PRP antibody concentrations.

The implementation of a new vaccine presents practical concerns, one of which is the present requirement to give *H influenzae* type b immunisation by separate injection. This was not a significant problem in our study as demonstrated by the high level of recruitment (75%) and the lack of dropouts. Preliminary observations from an implementation study now underway in the Oxford region suggests that vaccine uptake is minimally affected by the extra injection. However, studies are underway in which *H influenzae* type b and diphtheria, pertussis, and tetanus immunisations are given in the one syringe; in Finland, it is part of normal clinical practice to do so.

Although the initial response of young infants to PRP-T vaccine is clearly effective, the longevity of the protection is an important question and affects whether booster doses are required. Studies in Finland of PRP vaccine suggest that a serum anti-PRP antibody concentration of at least 1 μg/ml correlates with long term protection.[4] Given that over 90% of infants achieved antibody concentrations greater than 1 μg/ml, it is not certain that a booster dose will be required. In any case, it may be that the three dose course primes for a boostable (and thereby protective) response regardless of the absolute serum antibody concentration when the child is later exposed to *H influenzae* type b organisms.[17] This question may abe addressed by long term follow up of antibody concentrations and ideally by an efficacy trial with vaccinations given at 2, 3, and 4 months of age but without a booster dose in the second year of life.

Epidemiological surveillance in Oxford has shown that, of *H influenzae* type b disease in children under 5 years, only 6% occurs in those under 4 months whereas 42% occurs before 12 months (unpublished data). This illustrates the rapid increase in risk of infection as maternally derived antibody declines. Given 95% vaccine uptake in the new 2, 3, and 4 month schedule, immunisation has the potential to prevent up to 90% of *H influenzae* type b infections in young children. This translates to the potential annual prevention of 60 deaths and 1170 cases of infection in the UK.[2] The encouraging immunogenicity and tolerability of PRP-T conjugate vaccine, demonstrated in this study, make it a candidate for inclusion in the routine national schedule. An open intervention study of PRP-T vaccine given at 2, 3, and 4 months of age is underway in the Oxford region. It is anticipated that 30 000 infants will be immunised and that clinical efficacy can be evaluated by late 1992 when immunisation against *H influenzae* type b disease is due to start in the national programme.

We are grateful to all the families who participated in the study and we are thankful for the support and materials provided by Dr J Roberts and Dr B Fritzell of Merieux UK and Pasteur-Merieux Serum et Vaccins respectively. We also thank Dr H Kayhty and Miss L Saarinen for performing the radioimmunoassays and Miss Emma Wills for typing the manuscript.

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Archives of Disease in Childhood 1992; 67: 479–481

Raised serum soluble interleukin-2 receptor concentrations in cystic fibrosis patients with and without evidence of lung disease

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Accepted 4 December 1991

Abstract

Soluble interleukin-2 receptor (sIL-2R-CD25) concentrations were measured in the sera of 115 children with cystic fibrosis and 45 aged matched controls. Above the age of 4 years children with cystic fibrosis had significantly raised concentrations irrespective of disease status as judged by Shwachman score, lung function, or evidence of pseudomonas colonisation. It is believed that these data indicate that T lymphocyte activation can be detected before there is clinical evidence of lung inflammation due to infection in cystic fibrosis. They support the notion that early use of anti-inflammatory (immunosuppressive) drugs may have a role in delaying the progress of lung damage in cystic fibrosis.

There is increasing evidence that immune mediated inflammation is at least partly responsible for progressive lung damage in cystic fibrosis. Immune complexes wtih *Pseudomonas aeruginosa* antigen and autoantibodies found in the serum, sputum, and the tissues, high levels of elastin cleavage products in urine, and elastolysis in lungs all correlate with disease severity. These findings provide strong evidence that immunologically mediated tissue injury occurs in patients with cystic fibrosis and advanced lung disease.[1–4]

Continuous antigenic stimulation can have two consequences in cystic fibrosis, one being temporary immune unresponsiveness, and the other being a chronic hypersensitivity reaction or excessive immune response.[5] This excessive response is reflected in the form of high concentrations of serum immunoglobulins, neutrophil elastase, immune complexes, and a high incidence of detectable autoantibodies.[1–5] All of these abnormalities are seen in patients with severe lung disease long after the clinical and lung function findings indicate the presence of lung involvement. However it is known that inflammation and mild obstructive ventilatory defects occur early, before heavy lung infection is obvious.[1 5] For this reason we wished to identify a more sensitive marker of this early inflammation which could be used to assess progress and the severity of disease.

As T lymphocytes have a central role in the orchestration of immune responses, we decided to investigate one index of T cell activation. Interleukin-2 (IL-2) known as T cell growth factor induces the proliferation of not only the T cells but also lymphokine activated killer cells. It also has the effect of enhancing natural killer activity.[6–14] IL-2 induces the expression of its own receptor. This receptor is expressed on several mononuclear cells including T cells. Human peripheral blood mononuclear cells when activated in vitro were shown to release a soluble form of IL-2 receptor (sIL-2R) into the tissue culture supernatants, and in this form it may have an immunoregulatory function.[9] This sIL-2R is the part of the receptor shed into the circulation, which lacks the transmembrane and cytoplasmic portion.[6–13] There are detected concentrations in the serum of normal individuals, and raised concentrations have been found in autoimmune disease, transplant rejection, acute eczema, lymphoma, and leukaemia relapses.[15–17]

We have therefore investigated the sIL-2R concentrations in patients with cystic fibrosis with regard to their clinical findings to show the relationship of T cell activation to the outcome of the disease.

Patients and methods

A total of 177 blood samples were obtained from 115 patients with cystic fibrosis during their yearly assessments. On the same day chest radiographs and (where possible) lung function tests were performed. The presence of pseudomonas colonisation and acute infection was noted with simultaneous clinical evaluation of the patient by Shwachman score.[18] The scoring was done by two clinicians independently and the average of the two scores recorded. Diagnosis of acute infection was based on the clinical findings in addition to raised white cell count and C reactive protein concentrations. The blood samples were analysed for serum sIL-2R, IgA, IgG, IgM, and IgE concentrations. Serum sIL-2R concentrations were studied using a sandwich enzyme immunoassay cell-free soluble IL-2 receptor kit (T Cell Sciences Inc). The method was applied according to the instructions of the manufacturer.

sIL-2R concentrations were correlated with (i) lung function parameters, (ii) total lung capacity by plethysmography minus that measured by helium dilution as a measure of gas trapping (TLC-VA), (iii) forced expiratory flow at 50% of vital capacity from a flow-volume loop (FEF 50%) and forced vital capacity (FVC), (iv) serum immunoglobulins, and (v) Shwachman score. The effect of acute infection and presence of pseudomonas colonisation on sIL-2R concentrations were also assessed.

Control samples were obtained, with the consent of the parents, from 45 children attending the Paediatric Day Surgery Unit at Southampton General Hospital for routine

Table 1 sIL-2R concentrations (U/ml) in controls and patients with cystic fibrosis with regard to acute infection and/or pseudomonas colonisation Results are mean (SD)

Age groups (years)	*Patients*	*Controls*	*Acute infection*		*Pseudomonas colonisation*	
			With	*Without*	*With*	*Without*
0–3·9	1105·[illegible] (335·1) [n=10]	851·9 (334·3) [n=16]	1205·0 (340·6) [n=2]	1080·6 (349·7) [n=8]	1133·3 (335·0) [n=3]	1093·6 (361·2) [n=7]
	p=0·068		p=0·69		p=0·65	
4–7·9	828·1 (234·5) [n=40]	503·9 (91·1) [n=9]	816·7 (312·5) [n=14]	903·0 (319·6) [n=26]	872·9 (318·1) [n=19]	876·8 (321·8) [n=21]
	p=0·0038†		p=0·43		p=0·63	
8–11·9	739·9 (263·5) [n=48]	490·0 (78·3) [n=10]	778·6 (228·5) [n=12]	804·9 (284·4) [n=36]	753·9 (209·2) [n=21]	834·6 (308·4) [n=27]
	p<0·0005†		p=0·71		p=0·63	
≥12	827·9 (337·8) [n=79]	370·0 (138·3) [n=10]	959·6 (350·4) [n=33]	719·7 (292·8) [n=46]	806·1 (338·5) [n=46]	813·2 (321·4) [n=33]
	p=0·0005†		p=0·0021†		p=0·81	

†Significant differences

surgical procedures. The children did not have any history of asthma, eczema, hay fever, any known allergies, or recent infection. They all had normal concentrations of C reactive protein. The data on serum sIL-2R concentrations were analysed in four different age groups both in patients and controls. The age groups were separated as follows: group 1: 0–3·9 years, group 2: 4–7·9 years, group 3: 8–11·9 years, and group 4: ≥12 years.

Statistical analyses were done by minitab computer program using correlation analysis and Mann-Whitney test. The significance values were given in tables of relevant data.

Results

The mean (SD) sIL-2R concentrations of patients with cystic fibrosis was 840 (320·4) U/ml with a median of 790·0 U/ml. The breakdown of these data into age groups compared with controls are shown in table 1 and fig 1. There was no significant statistical difference between patients with cystic fibrosis and controls in the first age group. sIL-2R concentrations were significantly higher than controls in all groups after 4 years of age. Serum sIL-2R concentrations were not significantly different in patients with and without pseudomonas colonisation in all age groups. Similarly there were no differences in children under 12 years of age with and without acute infection. However, the patients with cystic fibrosis above 12 years of age with acute infection had significantly higher concentrations of sIL-2R than those without acute infection (p=0·0021) as shown in table 1 and fig 2.

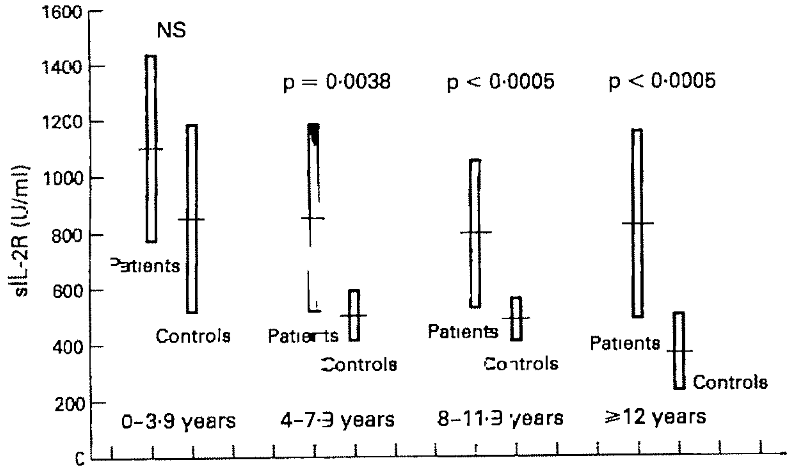

Figure 1 Comparisons of serum sIL-2R concentrations in patients with cystic fibrosis and age matched control children Statistical analysis by Mann-Whitney test.

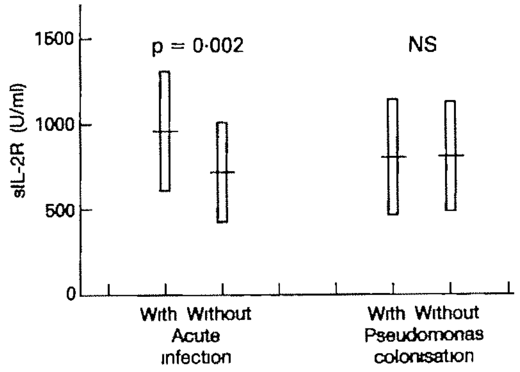

Figure 2 Comparison of serum sIL-2R concentrations in patients with cystic fibrosis above 12 years of age with and without acute infection and pseudomonas colonisation. Statistical analysis by Mann-Whitney test

Table 2 Correlation of sIL-2R concentrations and various clinical parameters

	r Value
Shwachman score	−0·17
TLC-VA	−0·019
FVC	0·151
FEF 50%	−0·097
IgE	−0·121
IgA	0·048
IgM	−0·019
IgG	−0·032

Shwachman scores and sIL-2R concentrations recorded simultaneously showed no correlation (correlation coefficient r=−0·16, p>0·05). In addition to this, sIL-2R concentrations showed no correlation between different parameters of lung function TLC-VA, FVC, FEF 50%, and IgE, IgA, IgM, and IgG concentrations as shown in table 2.

Discussion

In patients with cystic fibrosis many immunological abnormalities due to continuous antigenic stimulation of the immune system have been reported.[1–5] Our findings of significantly raised concentrations of sIL-2R are new and are probably a reflection of sustained T cell activation in these patients. As sIL-2R varies with age and is especially high in early childhood, perhaps due to the normally higher lymphocyte count, we analysed our data grouping the patients into different age groups.[17] The sIL-2R concentrations only just failed to show a significant difference between patients and controls under the age of 4 years but the differences were highly significant in older children (table 1). These data provide yet more evidence of an excessive immune response in patients with cystic fibrosis.

Superficially it seems that the lack of correlation between sIL-2R and clinical scores and the presence of pseudomonas colonisation, lung function abnormality, or raised immunoglobulins, does not comply with the hypothesis of immunologic lung injury in cystic fibrosis. However, raised concentrations of sIL-2R may be the first indicator of a developing inflammatory process, which increases even more during acute infection. With time the chronic inflammation produces changes in other immunological indices further down the activation pathways, such as immunoglobulin increases,[19] raised C reactive protein concentrations, and the release of neutrophil granule products,[20] which produce and therefore correlate with the increasing severity of disease.

sIL-2R is known to bind IL-2 efficiently competing with receptor on the cell surface and therefore may have a role in downregulating IL-2 dependent lymphocyte function.[21] Moreover, the rapid increase in sIL-2R after cellular activation may reduce receptor density on the cell surface below the critical threshold level reducing further lymphocyte proliferation. Increased sIL-2R concentrations may be the first sign of airway colonisation and inflammation that will eventually lead to an excessive immune response and lung damage. Even if sIL-2R is part of a compensatory response it is inadequate to overcome the enormous stimulation produced by the massive antigenic load of organisms which are never completely cleared from the airway.

These data support the fairly recent therapeutic recommendation of the use of anti-inflammatory drugs in cystic fibrosis. Steroids have been shown to delay deterioration even in young patients with cystic fibrosis but have not become part of routine protocols due to potential side effects.[4] These preliminary cross sectional observations confirm the role of the host immune response even at an early stage in the development of lung damage in cystic fibrosis and suggest that the early use of non-steroidal anti-inflammatory drugs may be important in the prevention of progression of disease. However longitudinal studies are now required to establish whether high concentrations of sIL-2R are associated with faster deterioration in lung function and whether therapeutic intervention has an effect on concentrations and clinical state.

Thanks to the Cystic Fibrosis Research Trust for financial support of the study

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Archives of Disease in Childhood 1992; 67: 482–487

Respiratory status and allergy after bronchiolitis

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Abstract

As part of a long term prospective study, 73 children who had been admitted to hospital with viral bronchiolitis as infants, were reviewed 5·5 years later and compared with a carefully matched control group. In the postbronchiolitis group, there was a highly significant increase in respiratory symptoms including wheezing (42·5% v 15·0%, relative risk=2·8).

Although atopy in the family was not significantly increased in the index group, personal atopy was more prevalent. However, personal atopy was not significantly more prevalent in the symptomatic postbronchiolitis, compared with those who were symptom free, and so did not account for the high prevalence of postbronchiolitis wheezing in this cohort. In addition, in a stepwise logistic regressional model, bronchiolitis remained a significant predictor of wheezing after adjusting for potential confounding variables, including atopy Bronchial responsiveness to histamine was significantly increased in the index group. However, no significant relationship of positive tests to wheezing could be demonstrated, and a high rate of positive responses was noted in the controls.

There have been many follow up studies of children who have acute bronchiolitis in infancy. All are agreed that these children are more likely to experience respiratory symptoms, particularly coughing and wheezing, compared with the normal population. Although more prevalent, these symptoms have varied in severity[1–3] and have tended to diminish with time.[4,5] Our own long term prospective study of bronchiolitis has shown that 75% experienced wheezing in the first two years after the illness[6] and 59% were still having wheezing episodes 3·5 years later.[7] What remains unclear is whether viral bronchiolitis *per se* causes increased airways lability[4,8] or whether those children with a genetic predisposition to atopy are more likely to develop bronchiolitis and/or postbronchiolitis symptoms. Previous studies looking at this issue have mostly been retrospective and have involved a single follow up study many years later,[1,3,4,8,9–12] thus potentially resulting in problems of recall bias. In some instances, follow up has been at a variable time interval since the illness and sometimes a control group has not been included.[1,9–12,15] The findings have been contradictory on the role of atopy,[1,4,14,16–18] and have suggested that environmental factors such as family size,[4,13,19] parental smoking,[1,9,18,20,21] breast feeding,[13,19] and neonatal respiratory illness[18,19] may be contributing to either the initial illness, subsequent symptoms, or both. There are also claims that bronchiolitis in infancy contributes to chronic airways obstruction in adult life.[22–24] In order to investigate these aspects further, we have reassessed the same cohort[7] 5·5 years after the illness and compared these children with a carefully matched control group and report the findings in this paper.

Patients and methods

One hundred and one patients were recruited on admission to the Queen's Medical Centre, Nottingham, during the winter epidemics of respiratory syncytial virus (RSV) infection in 1979, 1980, and 1981. The criterion for entry was the clinical diagnosis of acute bronchiolitis in a child with no history of a previous similar illness. All had cough, tachypnoea, and feeding difficulties associated with hyperinflation, recession, fine crepitations, and often rhonchi. The mean age at the time of admission was 113 days (range 25–343), and in those followed up 5·5 years later was 103 days (range 25–343). The first 21 children enrolled for the study were those whose illness was severe enough to preclude oral feeding. All subsequent admissions irrespective of severity were considered eligible. The original cohort included 54 males and 47 females, of whom 57/86 (66%) were RSV positive. This was assessed by immunofluorescence, tissue culture, or both. Of those followed up 5·5 years later, 42/62 (68%) of those with available results, were RSV positive.

The controls were recruited by obtaining roll lists from the schools in the catchment area of the hospital and matching each index child in terms of birth date, sex, race, area, and maternal smoking. The most important exclusion criterion for the controls was when it was not known whether they had suffered from acute bronchiolitis in the first year of life. Therefore children who had required admission to hospital in infancy with a diagnosis of acute bronchiolitis or required visits to their general practitioner for an ongoing respiratory problem in infancy, were not included in the control group. A history was taken from the mother with emphasis on details of upper and lower respiratory tract symptoms over the preceding year.

The family history of asthma, eczema, or hayfever was recorded, as were manifestations of atopy in the child such as eczema and allergies. The children were examined and recordings of height and weight were taken.

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Accepted 15 December 1991

Table 1 Clinical details, and social and family characteristics

	Bronchiolitis	*Control*	*p Value*
Mean (SD) birth weight (g)	3040 (630)	3160 (600)	NS
No (%) birth weight			
<2500 g	13 (7 8)	7 (9 6)	NS
<2000 g	2 (2 7)	5 (6·8)	NS
Mean (SD) gestation (weeks)	39 1 (2 2)	39·6 (1 6)	NS
No (%) <37 weeks	7 (9·6)	7 (9 6)	NS
No (%) breast fed	30 (41·1)	27 (37·0)	NS
Mean (range) length of breast feeding (weeks)	8·7 (0·5–36)	8 3 (0 5–26)	NS
Follow up:			
Mean (SD) weight (kg)	20 4 (3 4)	21 2 (2 8)	NS
Median weight centile	49	52	NS
Mean (SD) height (cm)	113·7 (5·4)	115 9 (4 9)	p<0·05
Median height centile	48	50	NS
Family:			
Mean (range) No of siblings			
Total	1·9 (0–6)	1 8 (0–6)	NS
Older	1 4 (0–6)	0·9 (0–4)	p<0 05
No (%) parents who smoke			
Mothers	40 (54 8)	41 (56·2)	NS
Fathers	35 (47 9)	39 (53·4)	NS
No (%) social class:			
1, 2	7 (9·6)	3 (4 1)	
3	35 (47·9)	32 (43 8)	
4	9 (12·3)	11 (15 1)	NS
5 and unclassified*	22 (30 1)	27 (37 0)	

*Unclassified=unemployed, disabled, single parent family

Skin tests were performed using the epicutaneous prick method[25] with three Bencard solutions—cat fur, house dust mite, and B2 grass pollens—along with a positive (histamine) and negative (saline) control. The weal diameter was measured at 15 minutes and a reading of 3 mm or more was regarded as positive. Lung function tests were performed using a PK Morgan spirometer and forced expiratory volume in 0·75 and 1 second ($FEV_{0·75}$, FEV_1) and maximum expiratory flow ($\dot{V}_{max}$) were recorded after an initial training period. A histamine challenge was performed where $\dot{V}_{max}$ was reproducible over three successive attempts. The technique described by Cockroft *et al* was adopted after dilution by buffered histamine acid phosphate in doubling concentrations from 0·25 to 8 mg/ml.[26] The provocative concentration of histamine required to cause a greater than 20% fall in $\dot{V}_{max}$ was recorded and the PC_{20} calculated.

STATISTICAL ANALYSIS

Results were analysed using the χ^2 test (with Yates's correction when $n<100$) for categorical variables, and the Fisher's exact test was used when the expected frequency for any cell was less than 5. The unpaired *t* test was used for continuous variables and the Mann–Whitney U test for variables that were not normally distributed and for some grouped data (height and weight centiles). The BMPD statistical package for stepwise logistic regression was used to assess whether the bronchiolitis/wheeze relationship remained significant after taking account of potentially confounding variables.

ETHICS

The study was ethically approved by the hospital ethics committee and written informed consent was obtained from the parents.

Results

Twenty eight children were lost to follow up. Of these, 21 had moved out of the area or had been lost to follow up despite repeated letters and telephone calls. Seven children were excluded: four because of major neurological illnesses, one because of congenital heart disease, and two on the basis that the original diagnosis was doubtful. Thus, 73 children, 36 males and 37 females, were seen at a mean age of 71 months (range 67–83 months) and a mean time since the illness of 67 months (range 65–78 months). The 73 controls were seen at a mean age of 75 months (range 68–74 months); thus, they were on average 4 months older than the index children when seen. The children in both groups were analysed according to clinical details along with social and family characteristics (table 1). The mean birth weight and gestation were not significantly different and there was no difference with respect to the frequency or duration of breast feeding. At the follow up visit, index children tended to weigh less and were significantly shorter than controls. However, when adjustment was made for the age difference between the two groups, there was no difference in their respective growth centiles. The mean number of siblings was not different, although index children had significantly more older siblings. The social class profile of the two groups was very similar. The groups were closely matched for maternal smoking, thus 55% of index children had mothers who smoked compared with 56% of controls. Paternal smoking was similar in the two groups.

At follow up 42·5% of the postbronchiolitis children reported wheezing episodes over the previous year compared with 15·1% of the controls, giving a relative risk for wheezing 5·5 years after the illness of 2·8 (table 2). Coughing episodes were reported in 65·8% of the index children and 37% of the controls, with a relative risk for postbronchiolitis of 1·8. With both symptoms, the differences between the two groups were highly significant (table 2). All of the children who reported wheezing episodes

Table 2 Respiratory symptoms, medication, and general practitioner consultations in the previous year. Figures are number (%) in each group, unless otherwise stated

	Bronchiolitis (n=73)	*Controls (n=73)*	*Relative risk*	*p Value*
Wheeze	31 (42·5)	11 (15 1)	2 8	p<0 001
Coughing episodes	48 (65·8)	27 (37·0)	1 8	p<0 001
Medication for episodes of cough/wheeze:				
Cough linctus	10 (13 7)	8 (11 0)	1 3	NS
Bronchodilators	24 (32·9)	4 (5·5)	6 0	p<0·0001
Prophylactics	7 (9·6)	3 (4 1)	2 3	NS
Antibiotics	28 (38·4)	17 (23·3)	1 6	p<0·05
Mean (range) No of URTI	3·8 (0–12)	2 7 (0–12)	—	p<0 05
Recurrent nasal blockage or discharge	25 (34·2)	8 (11·0)	3 1	p<0·001
Mean (range) No visits by general practitioner	1·7 (0–10)	1 1 (0–8)	—	p<0 05

Table 3 Personal and family history of atopy. Figures are number (%)

	Bronchiolitis	*Controls*	*p Value*
Family history of asthma in first degree relative	18 (24·7)	18 (24·7)	NS
Family history of asthma, eczema, or hayfever in first degree relative	38 (52·1)	32 (43·8)	NS
Personal history of eczema	15 (20·5)	8 (11·0)	NS
Positive skin tests:			
House dust mite alone	5 (6·8)	5 (6·8)	NS
≥1 positive tests	[illegible] (29·2)	11 (15·3)	p<0·05
≥2 positive tests	1 (16·9)	5 (6·8)	NS
Personal atopy (eczema and/or positive skin tests)	27 (37·0)	15 (20·5)	p<0·05

were also troubled with coughing. In the index group, 39·5% of those who had been RSV positive reported subsequent wheezing, compared with 36·5% of those who were RSV negative, thus demonstrating no difference between the two groups.

Upper respiratory tract infections (URTI) were reported as precipitants of wheezing in all symptomatic children (index and control). In addition, 18 (24·7%) of the index group and seven (9·6%) of controls reported exercise-induced wheezing (p<0·05). Allergen associated wheezing provoked by animals, grasses or food, was reported in five (6·8%) of the index children and two (2·7%) of controls. This difference was not significant Wheezing only in association with URTIs and/or changes in the weather was reported in 13 (17·8%) of the index children and three (4·1%) of controls (p<0·01).

There was a highly significant difference in the number of index children who used bronchodilator therapy over the previous year (32·9% of index children compared with 5·5% of controls, p<0·0001). Significant differences were also seen in the numbers who were prescribed antibiotics for respiratory symptoms. More of the index children were on asthma prophylactic therapy (sodiùm cromoglycate or beclomethasone dipropionate), 9·6% compared with 4·1%, but this difference failed to reach significance. The parents of index children reported significantly more URTIs and general practitioner consultations for respiratory illness in the past year, compared with the controls.

Index children reported persistent or recurrent nasal blockage in 34% of cases compared with 11% of controls, which was a highly significant difference. Of the 73 children who were seen at the 5·5 year follow up, 70 of these had been reviewed two years earlier. At that time, 39 (55·7%) were having wheezing episodes. Over the subsequent two year period, 14 of these had become wheeze free, and four children began wheezing when they had not been troubled previously. Thus, there remained a significant overall reduction of 25·6% in the reporting of wheezing between the two visits (p<0·0001). As regards coughing episodes, 36 (51·4%) reported coughing at both visits. By the 5·5 year follow up, 13 children who had previously had coughing were no longer troubled, but 10 were coughing when they had not previously done so. Thus, there was no overall significant reduction.

The frequency of asthma in first degree relatives was identical in the two groups (table 3). There was no significant difference in the incidence of asthma, eczema, or hayfever between index and controls in first degree relatives (52·1% *v* 43·8% respectively). Eczema was more commonly reported in the index children, but this was not significant. However, significantly more children had one or more positive skin test results in the index group (29·2% compared with 15·3% in controls) and when eczema and/or positive skin tests were combined as an index of personal atopy, this also was significantly more prevalent in the index group. Thus, personal atopy was related to bronchiolitis in our cohort.

When the relationship between bronchiolitis and subsequent wheezing was studied (table 4) the findings were interesting. Among the index children with positive skin tests, 47·4% of them had subsequent wheezing. However, 41·3% of those who did not have positive skin tests also reported wheezing. This suggests that atopy does not account for the high prevalence of wheezing 5·5 years after bronchiolitis.

The effects of parental smoking and breast feeding were also examined (table 5). Paternal smoking appeared to have no effect on the relative risk of wheezing before bronchiolitis. Children in the index group who had smoking mothers had a relative risk of 4·1 for wheezing compared with 1·8 for those with non-smoking mothers. This suggests that maternal smoking may be influencing the rate of wheezing after

Table 4 Children reporting wheezing related to atopic background Figures are number (%) in each group, and relative p values

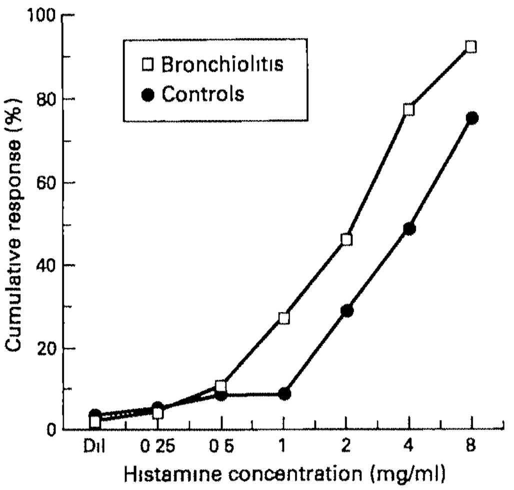
Wheezing children as proportion of total with:	*Bronchiolitis*	*Controls*	*Relative risk*	*p Value a v b*
Positive family history of asthma	(a) 11/18 (61·1)	(b) 7/18 (38·9)	1·6	NS
Negative family history of asthma	(c) 20/55 (36·4)	(d) 4/55 (7·3)	5·0	p<0·001
	(a) *v* (c) NS	(b) *v* (d) p<0·01		
Positive family history of asthma, eczema, or hayfever	(a) 21/38 (55·3)	(b) 10/32 (31·3)	1·8	p=0·08 NS
Negative family history of asthma, eczema, or hayfever	(c) 10/35 (28·6)	(d) 1/41 (2·4)	11·9	p<0·01
	(a) *v* (c) p<0·05	(b) *v* (d) p<0·01		
Eczema	(a) 10/15 (66·7)	(b) 4/8 (50)	1·3	NS
No eczema	(c) 21/58 (36·2)	(d) 7/65 (10·8)	3·4	p<0·001
	(a) *v* (c) NS	(b) *v* (d) p<0·05		
Positive skin tests (1 or more)	(a) 9/9 (47·4)	(b) 5/11 (45·5)	1·0	NS
No positive skin tests	(c) 19/6 (41·3)	(d) 5/16 (8·2)	5·0	p=0·0001
	(a) *v* (c) NS	(b) *v* (d) p<0·01		
Personal atopy (eczema/skin tests positive	(a) 14/27 (51·9)	(b) 5/15 (33·3)	1·6	NS
No personal atopy	(c) 16/42 (38·1)	(d) 5/57 (8·8)	4·3	p=0·0001
	(a) *v* (c) NS	(b) *v* (d) p<0·05		
Positive personal or family history of atopy	(a) 25/48 (52·1)	(b) 10/38 (26·3)	2·0	p<0·05
No personal or family history of atopy	(c) 6/23 (26·1)	(d) 1/35 (2·9)	9·0	p<0·05
	(a) *v* (c) p<0·05	(b) *v* (d) p<0·05		

Table 5 Children reporting wheezing related to parental smoking and breast feeding Figures are number (%) in each group

Wheezing children as proportion to total with	*Index*	*Controls*	*Relative risk*	*p Value*
Smoking mothers	(a) 20/40 (50 0)	(b) 5/41 (12 2)	4 1	$p<0\ 001$
Non-smoking mothers	(c) 11/33 (33 3)	(d) 6/32 (18 8)	1 8	0 29 NS
	(a) *v* (c) NS	(b) *v* (d) NS		
Smoking fathers	(a) 16/35 (45 7)	(b) 6/39 (15 4)	3 0	$p<0{\cdot}01$
Non-smoking fathers	(c) 15/38 (39·5)	(d) 5/34 (14 7)	2·7	$p<0{\cdot}05$
	(a) *v* (c) NS	(b) *v* (d) NS		
Breast fed	(a) 14/30 (46·7)	(b) 3/27 (11 1)	4 2	$p<0\ 01$
Not breast fed	(c) 17/43 (39 5)	(d) 8/46 (16·4)	2 3	$p<0\ 05$
	(a) *v* (c) NS	(b) *v* (d) NS		

Table 6 Lung function results Values expressed as % predicted for height and shown as mean (SD)

	Bronchiolitis	*Controls*	*p Value*
Peak expiratory flow rate	96 2 (15 0) [n=62]	97·8 (14 2) [n=68]	NS
FEV_1	96 4 (16·9) [n=61]	10·1 (18 2) [n=67]	NS
$FEV_{0\ 75}$	94 7 (17 7) [n=61]	99 9 (17 5) [n=67]	NS



Histamine challenge results.

bronchiolitis. However, when the rate of wheezing in the index group with and without smoking mothers was compared (50·0% *v* 33·3%), this relationship was not significantly different. Surprisingly, those who had been breast fed had a higher relative risk for wheezing than those who were not (4·2 *v* 2·3), suggesting that breast feeding does not protect against postbronchiolitis wheezing.

In a stepwise logistic regressional model, parental smoking, breast feeding, family history of atopy, personal atopy, family size, and social class were included. Having taken all these factors into account, bronchiolitis significantly improved the prediction of wheezing when added to the model ($p<0{\cdot}005$). When considering the index and control groups together, the factors that were significantly associated with wheezing overall, were family and personal history of atopy and bronchiolitis. Therefore, further analysis was performed looking only at these significant factors. In this model, bronchiolitis remained a significant predictor of wheezing ($p=0{\cdot}001$).

There was a non-significant trend for mean FEV_1, and mean $FEV_{0\ 75}$ to be lower in the index group (table 6). The difference in lung function results in those reporting wheezing compared with those who did not, also failed to reach statistically significant levels. Also, atopic children did not have significantly different lung function to non-atopic children in each group.

Histamine challenges were performed on 47 (64·4%) of the index group and 58 (79·5%) of the controls. Histamine challenges were not performed for the reasons shown in table 7. A high rate of histamine responsiveness was noted in the index group (table 8) with 77% having a PC_{20} of less than or equal to 4 mg/ml compared with 47% of the controls ($p<0{\cdot}01$). From the graph of the cumulative response to histamine it can be seen that there is a high rate of responsiveness in both groups, with the bronchiolitis group showing an excess of moderate responders, with no excess at concentrations of less than 0·5 mg/ml (figure).

Table 7 Reasons for not performing histamine challenges. Figures are number (%)

	Bronchiolitis	*Controls*
Lung function not reproducible	9 (12 3)	4 (5 5)
Unwilling	8 (11·0)	5 (6·8)
Home visit	5 (6 8)	3 (4·1)
Symptomatic (wheezy)	3 (4·1)	1 (1·4)
URTI	1 (1·4)	2 (2·7)
Total	26/73 (35·5)	15/73 (20·5)

Table 8 Bronchial responsiveness to histamine. Figures are number (%)

Provocative concentration	*Bronchiolitis (n=47)*	*Controls (n=58)*
Histamine ⩽1 mg/ml (moderate–severe response)	12 (25·5)	3 (5 2)
Histamine >1 mg/ml (mild response ⩽4 mg/ml)	24 (51 1)	24 (41 4)
Histamine >4 mg/ml (slight or no response)	11 (23 4)	31 (53·4)

Discussion

Two problems associated with a long term follow up such as this are, first, the number of the index children who cannot be traced and, secondly, providing a well matched control group. We were unable to trace 21 of the original 101 children. Attempts were made to phone those families who had failed to attend after at least two letters inviting them to come up with their children for assessment. When this too failed, the last known addresses of the families were visited. Wherever possible, we obtained forwarding addresses either from the present occupants, from local shops, or from the general practitioner. A further five were excluded on account of other neurological or cardiovascular disease, and two on the basis that the initial diagnosis was in doubt. An essential requirement for inclusion in the study was the presence of fine crepitations on auscultation on at least one occasion while in hospital. This undoubtedly excluded some children who had classic RSV bronchiolitis, but greatly reduced the chance of recruiting asthmatic infants whose acute attack was triggered by an RSV infection.

In these two children, we were unable to find any documentary evidence that they had ever had fine crepitations on auscultation.

The selection of a suitable control group also presented considerable problems. Ideally, we wished for the index and control children to be matched in all aspects apart from a previous episode of acute bronchiolitis. Selecting control children from birth records was considered but rejected on grounds that previous studies had shown an increased prevalence of parental smoking and low social class in those requiring admission for acute bronchiolitis. The groups were also matched very closely for breast feeding, the absence of this parameter being a criticism which had been levied against studies in the past.

We considered matching each index child with a control from his own class, but this proved impracticable, and so as a compromise, we selected schools close to the hospital, which were attended by the majority of the index cases. The children were then selected on birth date, sex, race, area, and maternal smoking. The led to very close matching for social class, parental as well as maternal smoking, breast feeding, and the incidence of prematurity. The control children as a group were significantly taller than the index children but were also 4 months older. Thus, their height centiles were not significantly different.

As previous studies have shown, there was a considerable excess of respiratory symptoms in the index cases, who had three times as much wheezing and twice as many coughing episodes as the controls. Those who were classified as RSV negative in the acute episode, as a result of immunofluorescent and paired serum, had the same pattern of symptomatology as those who were RSV positive. The high proportion of index children receiving both bronchodilator and prophylactic treatment, may well be related to their inclusion in this ongoing follow up study, but must to some extent be dependent on the frequency and severity of the symptoms in the index children. Although the overall prevalence of wheezing had fallen by 25% since the previous review 3·5 years after bronchiolitis, the prevalence of coughing was unchanged.

The frequency of asthma and other atopic symptoms was remarkably similar in the families of the index and the control groups, providing further evidence that those babies requiring admission to hospital with bronchiolitis do not have a genetic predisposition to asthma or increased bronchial reactivity. The data on personal atopy, was to some extent in conflict with this. There was a trend for more index children to have eczema and skin tests were significantly more likely to be positive in the index compared with the control group, the reverse of that found in the study by Pullan *et al*.[4] We have no adequate explanation for this discrepancy. In our cohort, babies were recruited who had the clinical features of acute bronchiolitis, whereas the Pullan study was restricted to those who were RSV positive. Inevitably, the index group would have included some babies destined to develop asthma and it is possible that in an attempt to avoid including babies who had had acute bronchiolitis in the control group, we excluded some who had infantile asthma. The number of babies excluded from the control group on these grounds was very small and not sufficient to explain the different prevalences of atopy.

Moreover, surprisingly, those children who had positive skin tests were no more likely to wheeze than those who had negative ones, again, suggesting that atopy was not an important cause of respiratory symptoms in the index children. Maternal but not paternal smoking was associated with an increased incidence of wheezing, but were were unable to show that breast feeding had a protective effect for post-bronchiolitic wheezing. Stepwise logistic regression analysis showed that acute bronchiolitis in infancy continued to have a highly significant effect on the incidence of wheezing, once maternal smoking, breast feeding, personal atopy, family size and social class, had been taken into account. A further analysis looking purely at family and personal history of atopy and bronchiolitis, again showed that bronchiolitis was acting as an independent factor, strongly supporting the contention that acute bronchiolitis is generating a state of abnormal bronchial reactivity in the airways rather than acting as a marker for children who have an inherent asthma tendency.

Baseline lung function tests were not particularly discriminatory but the histamine challenges did produce some interesting results. The incidence of extreme histamine sensitivity was very similar in the two groups. The main differences occurring in those who were moderately sensitive. We were concerned about the high incidence of positive responses in the controls, but this pattern of increased sensitivity in the young has previously been well documented.

From this study we conclude that although the incidence of wheezing falls in the fourth to sixth year after acute bronchiolitis, these symptoms remain considerably more frequent than in controls. Although the index children had more personal atopy, this was not related to respiratory symptoms. The data lends support to the hypothesis that acute RSV bronchiolitis is responsible for the production of an asthma syndrome which can persist for many years after the acute infection.

We gratefully acknowledge financial help from the National Asthma Campaign.

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Archives of Disease in Childhood 1992, 67: 488–490

Bronchial responsiveness in an area of air pollution resulting from wire reclamation

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Abstract

Spirometric data from 86 primary school children living in an area of air pollution resulting from wire reclamation incineration were analysed and compared with 92 non-exposed schoolchildren. There were lower values for forced vital capacity and forced expiratory volume and thus a higher incidence of pulmonary function abnormalities in the children in the polluted area than those in a non-polluted area. There was no significant difference in the prevalence of respiratory symptoms between these two areas when surveyed by a questionnaire. Twenty eight schoolchildren from a non-polluted area and 26 children from the polluted area, who were said to have no respiratory symptoms and for whom consent forms were obtained, were recruited for a bronchial responsiveness test. Nine (35%) of 26 children in the polluted area were responders (<50 U) and only one of the control subjects was a responder. The mean (SD) log cumulative dose producing a 35% decrease in respiratory conductance and the minimum cumulative dose required to decrease respiratory conductance from the baseline in the children of the polluted area were significantly lower than that of the control subjects (1·32 (0·37) log units and 1·26 (0·44) log units, respectively, compared with 1·70 (0·10) log unit for both measurements in non-exposed children). These results indicate that air pollution resulting from wire reclamation can produce a detrimental effect on both pulmonary function and bronchial responsiveness in primary schoolchildren who are continually exposed to air pollutants from the time of their birth.

Wire reclamation incineration is a source of environmental contamination. The resulting air pollutants include suspended particulates, nitrogen dioxide, sulphur dioxide, heavy metals, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, polychlorinated dibenzofurans, and dioxins.[1-3] These pollutants cause damage in the hepatic, dermatological, and immunological systems and may also cause fetal death.[4 5] In Taiwan, heavy metals are recovered for reuse by wire reclamation incineration. Wires were incinerated in an open area without using any pollution control equipment. The reclamation process has been performed for about 20 years in Wanli, a severely polluted area located in the southern part of Taiwan. Several years ago, the Bureau of Environmental Protection of Taiwan detected significant concentrations of dioxins and polychlorinated dibenzofurans in the air and soil of this area.[1] According to the governmental reports, there were also high morbidity and mortality rates due to chronic pulmonary disease in the Wanli area.[1] Previously, we found that the incidence of pulmonary function abnormality in children of the polluted areas was greater than that of the non-polluted area.[6] In order to investigate if long term exposure to air pollution resulting from wire reclamation incineration might have harmful effects on the airway reactivity, we compared the bronchial responsiveness of primary schoolchildren in the polluted area to those living in a non-polluted area.

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Accepted 12 November 1991

Methods

Children in the primary school in the polluted area of Wanli, near the incineration site, and in one school in a non-polluted area located in the centre of Tainan city were chosen for this cross sectional study. All children had been inhabitants in these districts since their birth, and their socioeconomic background was similar. By using a stratified and systematic sampling method, 100 sixth grade (12 year old) primary schoolchildren in these two areas were selected as subjects for study during April and June.

In addition to the air quality information provided by the Bureau of Environmental Protection of Taiwan, environmental air quality was evaluated by the concentrations of suspended particulates, nitrogen dioxide, and sulphur dioxide, of the air sampled from the two areas under study. The air sample for determining suspended particulates[7] was collected as previously described.[6]

All pulmonary function tests were administered in the schools by trained technicians using a portable spirometer (Microspiro-298, Chest). The procedure for performing forced spirometry was the same as our previous report.[6] The values of forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and forced expiratory flow between 25% and 75% of the forced vital capacity (FEV_{25-75}) were expressed as percentage of predicted values calculated by the equations of Polgar and Promadhat.[8] Abnormal spirometric parameters were defined as (a) FVC or FEV_1 of less than 80% of predicted values or (b) a ratio of FEV_1:FVC less than 75%.

A modified version of the ATS-DLD-78-C questionnaire[9] concerning the anthropometric data, socioeconomic condition, smoking history of the parents, and respiratory symptoms of the children was translated into Chinese and answered by the parents during home visits by trained personnel. Socioeconomic status (SES), derived from parents' occupation and education,[10] was divided into low (V and IV), middle (III), and high (II and I) categories. Chronic cough was considered to exist when a child frequently coughed for more than two years without apparent association with a common cold. Wheezing was considered to be present when it occurred with or without a common cold.

Because the inhabitants might fear that the government would prohibit wire reclamation incineration (one of their major sources of income) if the survey revealed unfavourable results, a bias in the parents' answers to the questionnare existed. So only those who replied that their children had no respiratory symptoms who completed consent forms had their children chosen for methacholine inhalation tests. Twenty eight schoolchildren from a non-polluted area and 26 children from polluted area were recruited from the study population for bronchial responsiveness evaluation.

Methacholine inhalation tests were carried out with an Astograph (TCK-6100, Chest) as previously described.[11] This machine can write dose response curves of respiratory resistance (Rrs) with tidal breathing during continuous inhalation of methacholine in twofold increment concentrations from 0·049 to 25 mg/ml every minute. Three indices were evaluated for the airway responsiveness in the present study: the baseline value of Rrs (Rrs-cont); the minimum cumulative dose required to start to decrease respiratory conductance from the baseline (D_{min}); and the cumulative dose producing a 35% decrease in respiratory conductance ($PD_{35}Grs$).

Results are presented as mean (SD) values. Statistical evaluations were performed by Student's *t* test. A p value below 0·05 was considered significant. Differences in prevalence of pulmonary function abnormalities and respiratory symptoms between these two groups were evaluated by χ^2 test. Statistical analyses of $PD_{35}Grs$ and D_{min} values were performed on logarithmically transformed data because they showed logarithmic normal distribution.[12]

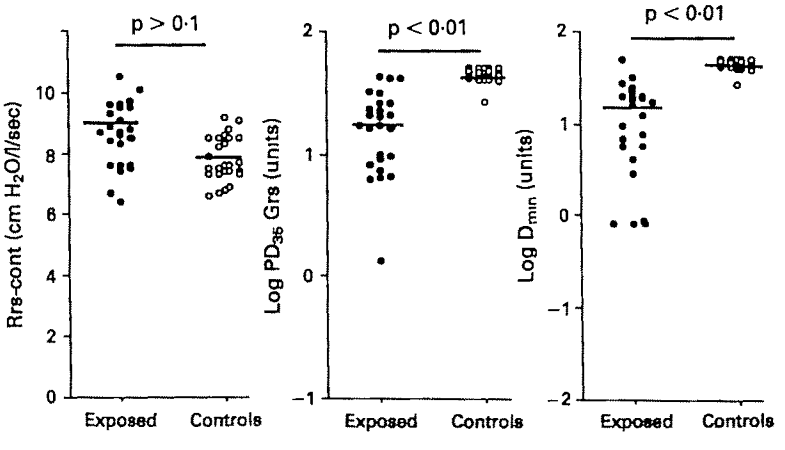
Results

In our study we found the polluted area had higher concentrations of sulphur dioxide and nitrogen dioxide than the non-polluted area which served as a control (sulphur dioxide 18·1 *v* 2·1 parts/billion (ppb); nitrogen dioxide 12·6 *v* 2·1 ppb).

Questionnaires were returned and spirometry was successfully performed by 86 children in the exposed area and 92 in the control area. Twenty two children were excluded because of grossly incomplete questionnaires and unacceptable spirometry. There were no significant differences in demographic characteristics between these two areas (table). In addition, no significant differences in the prevalence of respiratory symptoms surveyed by questionnaire between the polluted and non-polluted areas were noticed.

The distributions of pulmonary function abnormalities in the polluted group were 15·6% for FVC, 17·5% for FEV_1. In the control group, the distributions of abnormality were 6·5% for FVC, 3·2% for FEV_1. The incidence of pulmonary function abnormality in the polluted area was thus greater than that of the non-polluted area ($p<0·05$, χ^2 test). These results were the same as in our previous report.

The results of methacholine inhalation test are shown in the figure: baseline airway resistance (Rrs-cont), bronchial reactivity ($PD_{35}Grs$), and bronchial sensitivity (D_{min}). There was no statistical difference in Rrs-cont between these two groups. Takishima *et al*[12] defined the subjects who had a D_{min} of more than 50 U (or log D_{min} $>1·699$ log unit) as non-responders and the subjects who had a D_{min} of less than 50 U as responders. According to their criteria, nine (35%) of 26 children living in the polluted area were responders and only one of 28 children from the non-polluted area subjects was a responder. The mean (SD) log $PD_{35}Grs$ of the children of the polluted area was significantly lower than that of the non-polluted area (1·32 (0·37) log units and 1·70 (0·10) log units, respectively $p<0·01$). The mean (SD) log D_{min} of the children of the polluted area was significantly lower than that of the control subjects



Baseline respiratory resistance (Rrs-cont), bronchial reactivity ($PD_{35}Grs$), and bronchial sensitivity (D_{min}) in 26 children from the exposed area (solid circles) and 28 control subjects (open circles). A bar shows the mean value. Values of $PD_{35}Grs$ and D_{min} of more than 50 U were plotted as 50 U (log $PD_{35}Grs$ and log D_{min} of 1·699), and represent the non-responders whose respiratory resistance did not change throughout the methacholine inhalation test.

Demographic characteristics of the study children in polluted and non-polluted areas

	Polluted area	*Non-polluted area*
Sex· M/F	46/40	50/42
Height (cm): M/F	133·5/135·6	132·7/134·9
Weight (kg) M/F	29·8/31·2	30·1/31·6
SES (%)*·		
I	3·0	3·1
II	18·2	25·2
III	69·4	68·4
IV	9·4	3·3
Parents smoking (%):		
Father	33·6	31·5
Mother	0	0
Chronic cough	4·7	6·5
Chronic phlegm	3·5	4·3
Wheezing	2·3	3·3
Diagnosed asthma	2·3	3·3
Chest illness	8·1	6·5

*SES (socioeconomic status) derived from parents' occupation and education was divided into low (V and IV), middle (III), and high (II and I) categories.

(1·26 (0·44) log units and 1·70 (0·10) log units respectively, p<0·01).

Discussion

This study examined the bronchial responsiveness and pulmonary function of primary schoolchildren exposed to wire reclamation incineration. It is known that this industry is a source of environmental contamination. In our study, all the children in polluted areas have suffered from long term exposure to air pollution caused by outdoor wire reclamation incineration since their birth. Our results showed that children in the exposed area had a greater incidence of pulmonary function abnormality than the control children, both in the restrictive and obstructive types of abnormality. Moreover, we also found that the bronchial responsiveness was increased in children living in the exposed area compared with those of the controls (figure). This suggests that air pollutants resulting from wire reclamation incineration have an ill effect on pulmonary function in children.

Although the polluted area had higher concentrations of sulphur dioxide and nitrogen dioxide than the non-polluted area, we did not measure the levels of exposure to pollutants ascribable to the process of wire reclamation incineration due to the lack of equipment for these measurements. Nonetheless, the Bureau of Environmental Protection of Taiwan reported several years ago that wire reclamation incineration produced a lot of air pollutants,[1] including highly toxic substances such as polycyclic aromatic hydrocarbons, dioxins, and polychlorinated dibenzofurans in Wanli and its vicinity. Therefore, the impairment of pulmonary functions and an increase in bronchial hyper-responsiveness in exposed children might be due to the effect of air pollution resulting from wire reclamation incineration.

An analysis of epidemiological as well as animal studies leaves little doubt that air pollution aggravates respiratory problems. Atmospheric pollution by smoke, sulphur dioxide, and nitrogen dioxide may provoke progressive impairment of ventilatory function and airflow obstruction in control subjects and in asthmatic patients.[13] The effect of long term exposure to low or moderate concentrations of air pollutants has not been defined. Tseng and Li found that prolonged exposure to low concentrations of atmospheric sulphur dioxide might induce airway inflammation and bronchial hyper-reactivity and predispose to episodes of childhood asthma.[14] Sultz *et al* reported a significant correlation between levels of air pollution and the number of children hospitalised for asthma in Buffalo.[15] By contrast, Ware *et al*[16] reported that, for preadolescent children, exposure to moderately increased concentrations of pollutants—for example, from coal burning—would increase the risk of bronchitis and of other respiratory disorders, but has little or no effect on pulmonary function level. These studies suggest that long term exposure to air pollution might have a harmful effect on pulmonary function in children or asthmatic patients.

Our results were consistent with our previous report[6] that there were no significant differences in the prevalence of chronic cough and wheezing. These results seemed to contradict the pulmonary function measurements. The possible explanation was the bias in answering the questionnaire due to the fear that the government would prohibit wire reclamation (a major employer) if the surveys revealed unfavourable results. The epidemiological approach to survey respiratory symptoms by questionnaire was somewhat crude. The major obstacle in investigations of this nature lies in the fact that morbidity and pollution data are usually held by local government officials in diverse disciplines. A complete environmental analysis and health prevalence study could meet with further resistance from the industry, economists, and local politicians.[17] Our results on bronchial responsiveness might provide further evidence of the impairment in pulmonary health in the children of the polluted area.

In conclusion, our results showed that air pollution resulting from wire reclamation incineration could produce a detrimental effect on both pulmonary function and bronchial responsiveness in primary schoolchildren who had been chronically exposed to the air pollutants since their birth.

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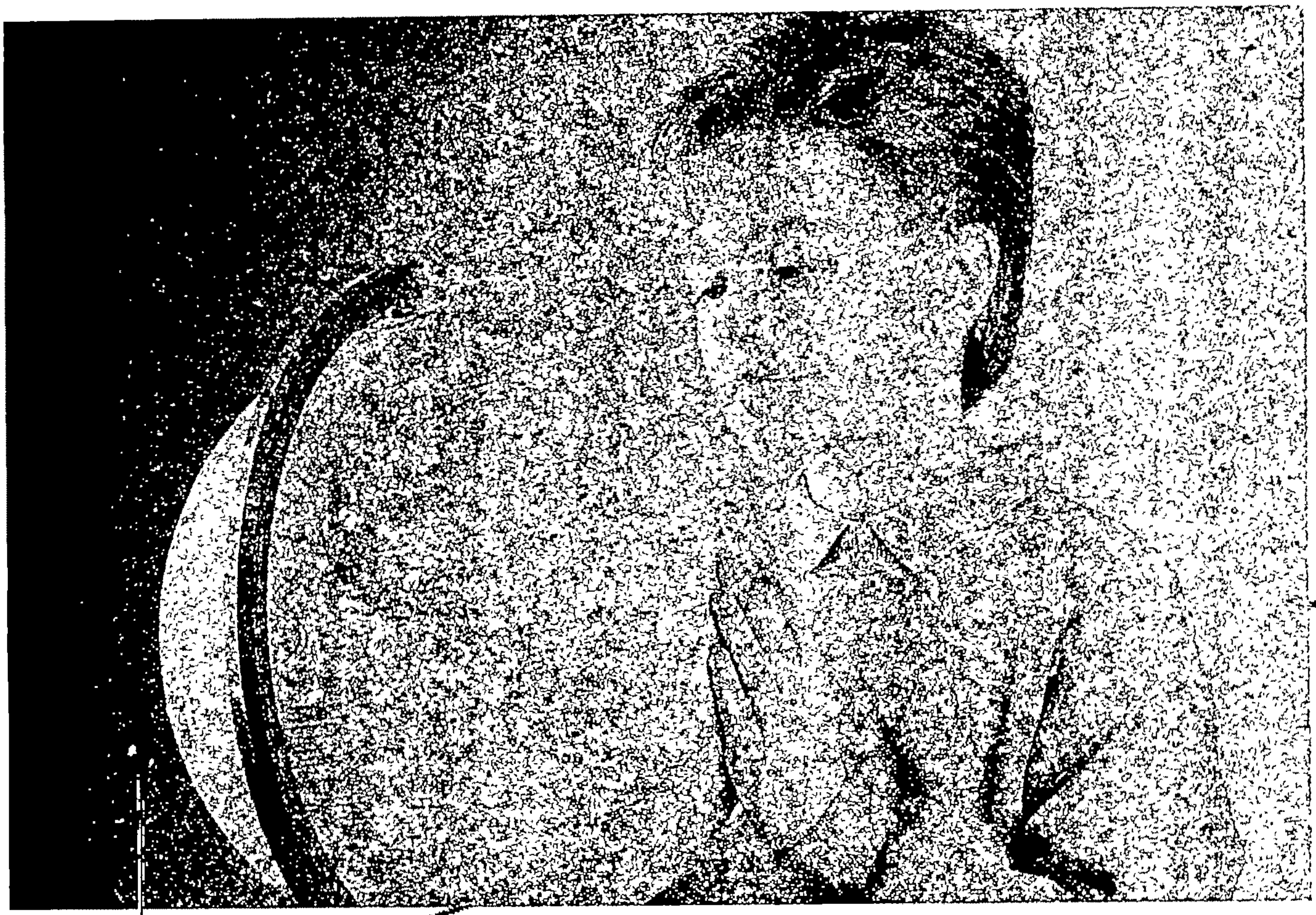

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Archives of Disease in Childhood 1992; 67: 491–495

Atopy, bronchial responsiveness, and symptoms in wheezy 3 year olds

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Accepted 10 December 1991

Abstract

Fifty children with at least one hospital admission for acute lower airway obstruction in the first 2·5 years of life were assessed at 3 years of age to determine the relationship between atopy, bronchial responsiveness, and the pattern of their symptoms. Bronchial responsiveness was measured by assessing the effect of inhaled metacholine, using the change in transcutaneous oxygen tension ($Ptco_2$) as an indirect measure of response. Symptom patterns were defined by the number of wheezing episodes associated with colds and the presence or absence of cough or wheeze unrelated to viral infections. Forty per cent of the children were found to be atopic by skin prick test or history. In contrast to the situation found in older children and adults, the non-atopic children had significantly greater bronchial responsiveness (lower mean concentration of methacholine causing a 20% fall in $Ptco_2$, the PC_{20}) than the atopic children and significantly more of them had an onset of respiratory symptoms in the first year of life. Cough and wheeze in the absence of colds was more frequently found in the atopic children as was the use of continuous medication. However, the number of reported acute episodes of wheeze associated with colds was the same in the two groups. The findings of the study suggest that in this hospital based group of children, acute wheeze associated with colds in the first three years of life is independent of the finding of atopy and that bronchial responsiveness in this age group may have a different pathogenesis from that in older subjects.

Recurrent acute episodic wheeze is very common in early childhood. It is usually associated with viral infections and is often described as 'post bronchiolitic' wheeze in the first two years of life. However, little is known about the natural history of wheezing and its relationship to atopy and bronchial responsiveness during the preschool period. Previous studies have usually selected a particular population of children at risk, for example, children of atopic families[1 2] or those who have experienced acute viral bronchiolitis in infancy.[3–5] Thus the relationship between recurrent post bronchiolitic wheezing and the development of atopic asthma, characteristic of older children, remains unclear. An additional problem has been the lack of a universally accepted definition of bronchiolitis; indeed the term is used differently on each side of the Atlantic. Clinically, a young child with an episode of wheeze after bronchiolitis caused by respiratory syncytial virus and a highly atopic child with an early episode of 'asthma' may both present with an identical, discrete episode of wheezing related to a viral infection. It has been suggested that both categories of children share a common factor which induces a predisposition to wheeze in association with viral infections that is independent of atopy, but that only those who develop airway sensitisation to aeroallergens will develop asthma in later childhood.[6]

The division of wheezy infants into two such distinct populations is still controversial. Some workers claim that all young wheezers should be considered as deriving from the same population and that any difference between them is merely one of severity.[7] Information currently available does not satisfactorily resolve this debate. A longitudinal population study of children born to atopic parents has shown a bimodal period prevalence of wheezing. Those wheezing before the age of 2 years rarely wheezed after that age, in contrast to those with an older age of onset in whom wheezing persisted and was strongly associated with atopy.[1]

It is important to ascertain whether or not subgroups of wheezers in fact exist as, if present, this could imply differences in underlying pathology and associated risk factors. Also, it is possible that, if prognosis and clinical outcome varies between subgroups, a different therapeutic approach, either in the short or long term, might be appropriate. Without considering various patterns of wheezing in young children separately, these important questions cannot be answered.

Therefore, in order to see if there exist subpopulations of young wheezers, which can be distinguished by the pattern of their symptoms, development of atopy or degree of bronchial responsiveness, a cohort of 50 children who had been admitted to hospital with an acute episode of lower respiratory obstruction (wheeze) during the first 2·5 years of life, was recruited. The intention was to include those with a diagnosis of bronchiolitis, recurrent post bronchiolitic wheezing, and 'wheezy bronchitis' as well as atopic children with early asthma. As part of a prospective study, these children were first seen as near to their third birthday as possible, and our findings form the basis of this report.

Subjects and methods

Children born between January 1986 and June 1987, who had been admitted to Hammersmith

Hospital with an episode of acute lower respiratory obstruction in the first 2·5 years of life were selected from the hospital records. The following diagnoses were included: bronchiolitis acute wheeze, wheezy bronchitis, and asthma Recruiting to the study continued until 50 children had been enrolled. They were seen as near as possible to their third birthday when the following assessments were made.

PERSONAL AND FAMILY HISTORY

The age of admission and clinical details including diagnosis were obtained from the hospital notes. A detailed written questionnaire was completed by a parent. This included information about parents and siblings concerning respiratory symptoms and their relationship to viral infections, allergies, and home conditions. For the index child, details were obtained about the medical and atopic history, and about respiratory symptoms including age of onset, relationship to viral infections, and other environmental stimuli. A positive history of atopy was defined as the presence of eczema, rhinoconjunctivitis to a known allergen, reaction to animal dander, or unequivocal food intolerance. A question was specifically asked about the estimated number of acute episodes of wheezing associated with viral infections and about the presence or absence of cough or wheeze in the absence of upper respiratory infections.

SKIN PRICK TESTS

These were performed using a specially designed device which held up to eight lancets (Phazet, Pharmacia). The device allowed multiple skin prick tests to be performed simultaneously, ensuring uniform skin penetration and maximal response.[8] Five lancets were used: one control, one histamine coated, and three allergen coated (*Dermatophagoides pteronyssinus*, cat, and timothy grass). As Phazets are not available for food allergens, an additional control lancet was placed over a drop of a wet preparation of egg extract (Merck Ltd). The maximal diameter of each skin weal was measured with a ruler after 15 minutes. The responses were read by the same observer throughout the study. A weal size of ≥2 mm was considered a positive response to allergen.

METHACHOLINE CHALLENGE

An interval of at least two weeks was allowed before the test after a clinical viral infection. All medication was witheld for 24 hours. The challenge was performed by administering methacholine sulphate aerosol for one minute through a Wright nebuliser using a mouth piece, with the nose clipped. The subject remained quietly seated throughout the study. The starting concentration of methacholine was 0·5 g/l and the inhalations were repeated at five minute intervals using quadrupling dilutions up to a maximum of 32 g/l. The same nebuliser was used for each subject with airfow of 7·5 l/minute. The output of the nebuliser was checked at intervals between subjects to ensure constancy. After the final concentration of methacholine, the child was given nebulised salbutamol in order to facilitate rapid recovery.

The response was assessed by monitoring the fall in transcutaneous oxygen tension ($Ptco_2$) using a skin electrode (Kontron) attached to the chest wall and heated to 44°C.[9] The electrode was calibrated in air (20·9 kPa). After application, an equilibration period of at least 20 minutes was allowed. Baseline measurements were made by taking records on the minute for eight minutes. After methacholine inhalation, a reading was taken at exactly 1, 2, and 3 minutes after each inhalation. The exact concentration of methacholine causing a 20% fall in $Ptco_2$ (PC_{20}) was calculated by interpolation using the last two points on the log concentration response curve.

An informed verbal and written consent was obtained from a parent and approval for the study was obtained from the hospital ethics committee.

ANALYSIS

The significance of differences between groups was assessed using a χ^2 test with a Yates's correction or one way analysis of variance, as appropriate. Correlations between factors were made using regression analysis. A p value of <0·05 was considered significant.

Results

Of the 50 children, 31 were boys. Their ethnic origins were: 29 white, six from the Indian subcontinent, and 15 were Afro-Caribbean. Details of their respiratory history, including age of onset, use of prophylactic medication, frequency of attacks, duration since last wheezing episode, and presence or absence of symptoms between viral infections are shown in table 1.

Table 1 Characteristics and pattern of lower respiratory symptoms for the group as a whole and the atopic and non-atopic children compared. Results are

	Male	Prophylactic medication			Age at index admission		Admission diagnosis		Age at onset of wheeze		Smoking mother	
		Nil	Inhaled steroids	Sodium cromoglycate	<1 year	≥1 year	Bronchiolitis	Asthma, wheeze, or wheezy bronchitis	<1 year	≥1 year	Yes	No
Atopic (n=20)	13 (65)	12 (60)	5 (25) **	3 (15)	6 (30)	14 (70)	11 (55)	9 (47)	8 (40) **	12 (60)	5 (25)	15 (75)
Non-atopic (n=30)	18 (60)	29 (97)	1 (3)	0 (0)	17 (57)	13 (43)	11 (37)	19 (63)	23 (77)	7 (23)	10 (33)	20 (66)
Total	31 (62)	41 (82)	6 (12)	3 (6)	23 (46)	27 (54)	22 (44)	31 (62)	19 (38)	15 (30)	15 (30)	35 (70)

Significance of difference between atopic and non-atopic children by χ^2 test: *p<0·04, **p=0·002, ***p<0·001

Table 2 Geometric mean methacholine PC_{20} in the 35 children who performed methacholine challenge. The results are shown for groups of subjects, divided according to characteristics and symptom patterns

	Admission diagnosis		*Atopic*	*Non-atopic*	*Interval since last symptom (months)*		*Reported number of attacks*		*Cough/wheeze between colds*		*Smoking mother*	
	Bronchiolitis	*Asthma, wheeze, or wheezy bronchitis*			*<6*	*≥6*	*1–6*	*>6*	*Yes*	*No*	*Yes*	*No*
No of children	17	18	17	18	20	15	12	22	21	14	9	26
Methacholine PC_{20}	4·3	4·3	6·7	2·8	4·8	4·8	5·1	4·1	5·1	3·7	4·3	4·3
Difference	NS		p=0·01		NS		NS		NS		NS	

NS=not significant.

ASSESSMENT OF ATOPY

A skin weal response to histamine of ≥ 2 mm was found in all children. None showed a response to the control of more than 1 mm. Eighteen children had a positive (≥ 2 mm) skin weal response to at least one allergen and in all except three of these children there was a definite atopic history. Two children with an atopic history had negative skin prick tests. Using the criteria of either a skin response of ≥ 2 mm to at least one allergen or a positive atopic history, 20 children were considered atopic.

RELATIONSHIP OF ATOPY TO PATTERN OF RESPIRATORY SYMPTOMS (TABLE 1)

There was no difference in the prevalence of atopy between the sexes or between those with an admission diagnosis of bronchiolitis or other types of wheezing (asthma, wheeze, or wheezy bronchitis). There was no difference in the number of acute wheezing episodes associated with presumed viral infection reported by the atopic and the non-atopic children. Significantly more atopic children had symptoms between viral infections (p=0·04) and were using continuous prophylactic medication (p<0·001). Non-atopic children were more likely to have had their first lower respiratory symptom under 1 year of age (p=0·02) and more had been admitted to hospital under 1 year of age (p=0·04).

METHACHOLINE RESPONSIVENESS

A methacholine challenge was successfully completed by 35 of the 50 children. One parent refused permission, there was a technical problem with one test, and the remaining 13 children were unable to cooperate.

In all the completed challenges, a PC_{20} of less than 32 g/l (the highest concentration used) was obtained. There was no significant difference in the geometric mean PC_{20} between boys and girls (table 2). Nor was there a difference in PC_{20} according to the season or the month of testing. The geometric mean PC_{20} was significantly lower (p=0·01) in non-atopic children than the atopic (table 2). There was no significant association between PC_{20} and (a) the presence or absence of symptoms between acute viral episodes, (b) the presence of symptoms within the preceding six months, or (c) maternal smoking (table 2).

Discussion

This study has considered the outcome, at 3 years of age, of a hospital based cohort of children with a history of wheeze. It differs from most previous similar studies in that the children were not preselected according to diagnosis or atopic family history. By the age of 3 years, 40% of the children were considered to show evidence of atopic sensitisation. Further children within the group are likely to become manifestly atopic as they grow older as atopic features increase with age.[1,9] It is not known whether or not atopy generated symptoms can precede skin sensitisation in this age group. The skin tests were performed by a well validated method[8] so technical problems are not likely to account for negative skin test results. In older children, a skin weal diameter of at least 4 mm has been recommended to describe a clinically significant atopic response.[10] Skin responses increase with age during childhood,[1,11,12] and in two of this group we were unable to obtain a histamine response greater than 2 mm despite repeated attempts. As there was a very close association between a positive skin prick test and an atopic history using this cut off point, a 2 mm weal is likely to be relevant in this age group, using allergen coated lancets. Two children with a positive atopic history had negative skin prick tests. In one of them the atopy was based solely on a history of eczema, which, it has been suggested, may be confused with seborrhoeic dermatitis.[1] It is possible that this one child was wrongly classified.

In this study of 3 year olds, a difference in the pattern of wheezing symptoms was discernable between the atopic and non-atopic children. The latter were more likely to have experienced the onset of symptoms within the first year of life while the atopic children more frequently reported symptoms between acute viral episodes. Chronic, as opposed to acute intermittent asthma, was also found by Zimmerman and colleagues to be more characteristic of highly atopic children who, like the atopic children in

number (%)

Interval since last symptom (months)			*Reported number of attacks*				*Cough/wheeze between colds*	
<1	*1–6*	*>6 m*	*1 or 2*	*3–5*	*6–10*	*>10*	*No*	*Yes*
12 (60)	5 (25)	3 (15)	1 (5)	3 (15)	3 (15)	13 (65)	6 (30)	14 (70)
11 (37)	6 (20)	13 (43)	6 (20)	4 (15)	8 (27)	12 (40)	19 (63)	11 (37)
23 (46)	11 (22)	16 (32)	7 (14)	7 (14)	11 (22)	25 (50)	25 (50)	25 (50)

this study, were more likely to be taking continuous prophylactic medication.[13] This difference in medication between atopic and non-atopic children could arise because those with a family history of atopy are more likely to be given prophylaxis. In the present study, both groups of children showed a tendency to experience recurrent episodic wheeze in association with clinical viral infections but the reported numbers of episodes did not differ between the two groups. This implies, as has been previously suggested, that in this age group, the tendency to wheeze in response to viral infections is independent of atopy.[1 6 14] Only 15% of the atopic children had been symptom free for more than six months compared with 43% of the non-atopic children. Although the differences were not statistically significant, this could indicate a trend that may become apparent with increasing age.

Bronchial responsiveness has not previously been assessed in a cohort of 3 year old children. As children in this age group are unable to cooperate with repeated measurements of lung function, we had to resort to using changes in Ptco$_2$ as an indirect measure of bronchoconstriction. Mochizuki *et al* found a good correlation between the threshold dose of methacholine as measured by changes in respiratory resistance and that measured by Ptco$_2$ in older and sedated preschool children.[15] In older subjects we found no significant differences in the methacholine concentration causing a 20% fall in Ptco$_2$ and that producing a 40% increase in respiratory resistance.[9] In a small number of normal adult subjects, the repeatability of the PC$_{20}$ values assessed by a fall in Ptco$_2$ was within one doubling dilution of methacholine, and similar to that calculated simultaneously using respiratory resistance.[9] It is not clear from the present results whether or not bronchial responsiveness in this group of children as a whole deviated from that of children without a history of wheezing. As population data were not available only a between group comparison was possible. Our finding that the non-atopic children were significantly more responsive to inhaled methacholine than the atopic children is the reverse of the situation found in older children and adults.[10 16 17] Recent viral infections and month of testing are unlikely to account for the difference as neither the interval since the last symptom nor the month of test were related to the PC$_{20}$. It could be argued that the reduced bronchial responsiveness in the atopic children was due to their increased use of topical steroid treatment (table 2). However, in adult asthmatic subjects the bronchial responsiveness was greatest in those taking regular inhaled steroids.[18] Variations in delivered concentration of methacholine to the lung due to air entrainment could not explain the difference as both groups were the same age.[19]

It is a possibility that in young children the relationship between bronchial responsiveness, respiratory symptoms, and atopy depends upon the population selected. For example, in a prospective study of infants of atopic parents, atopic sensitisation in infancy strongly predicted both appreciable hyper-responsiveness, when it was first assessed at 7 years, and an increased tendency to wheeze.[2] In contrast, in a follow up study of children with bronchiolitis in infancy assessed when aged 5–6 years, there was no relationship between either bronchial responsiveness and current wheezing (point prevalence 71%) or bronchial responsiveness and a family history of atopy.[5]

This apparent discrepancy between the two populations, which was also noted in older children by Clifford and colleagues,[11] might be explained by the findings of Crane and colleagues who performed a population cross sectional study of Tokelauan immigrant children aged between 5 and 13 years.[20] It was found that bronchial responsiveness was similar in atopic and non-atopic children of 5–6 years but became increasingly discrepant with age. The histamine PC$_{20}$ increased appreciably between the age bands 5–6 and 7–8 years in atopic children, but in contrast it gradually declined with age in the non-atopic children. This suggests that the pathogenesis of bronchial responsiveness may be different in atopic and non-atopic children. Its relationship to atopy will therefore depend on the population selected for study and the age of the child.

In the present study, bronchial responsiveness was assessed at a young age and the high level of responsiveness in non-atopic children could have reflected relatively smaller airways. We had hoped to include a measure of respiratory resistance using the forced oscillation technique. Unfortunately the majority of the children were unable to cooperate, so no direct measurement of airway function is available. Martinez and coworkers, assessing babies before their first respiratory symptom, found that those who subsequently developed lower respiratory symptoms with viral infections had the poorest lung function.[21] The association with preceding poor lung function was most noticeable in those in whom wheezing persisted into the second and third years of life.

Respiratory symptoms in very young children are associated with maternal or passive smoking.[22 23] In our study smoking in parents was not significantly related to symptoms or methacholine PC$_{20}$. As a surprisingly small number (30%) of parents admitted to being smokers (table 1) and as no objective measurements, such as cotinine concentrations were made, these findings may not be reliable.

The outcome of children said to have bronchiolitis during their index admission was no different from those given the diagnosis of asthma, acute wheeze, or wheezy bronchitis. Changing the criteria for a diagnosis of 'bronchiolitis' by only including those admitted under 9 months of age with appreciable chest hyperinflation and predominant fine crepitations (n=15) made no difference to outcome in terms of the number of reported subsequent acute wheezy episodes or the development of atopy.

This observation is in agreement with previous studies that have not found any difference in outcome between infants admitted with a variety of lower respiratory illnesses including bronchiolitis, both with and without respiratory syncytial virus isolation.[24] Therefore the term bronchiolitis would seem to have no significant epidemiological meaning, although it may be considered to constitute a definite clinical syndrome. The term post bronchiolitic wheeze may therefore be confusing as a description of early episodic wheezing as it implies a causal role between the first and subsequent illnesses.

The findings of this study are compatible with the proposal that the varying interaction of three factors—bronchial hyper-responsiveness, atopy, and an increased susceptibility to lower respiratory manifestation of viral infections—gives rise to the differing patterns of asthma seen during childhood.[6] The changing pattern of wheezing during early childhood could be explained by this hypothesis as follows. The early development of lower airway obstruction in relation to viral infections could occur in those with a combination of poor airway function (a probable determinant of increased bronchial responsiveness) and a particular susceptibility to viral infections. With age the size of the airways increases and viral infections become less frequent, so that the tendency to wheeze in response to viral infections will diminish, unless bronchial responsiveness is perpetuated by airway inflammation associated with atopy.

In addition, the results of this study suggest that although the number of acute wheezing episodes related to clinical viral infections in the first three years of life is independent of atopy, the tendency to wheeze between viral infections was associated with atopy. The finding of increased bronchial responsiveness in the non-atopic 3 year olds contrasts with the reverse situation reported in older subjects with asthma and lends weight to the idea of a different pathogenesis for bronchial responsiveness in the two age groups. By 3 years, however, it was not possible to define two distinct populations of wheezers, although differences were seen between the atopic and the non-atopic children. There were, however, sufficient differences to encourage other workers, with perhaps larger community based populations, to consider the possibility of a differing pathogenesis between acute episodic wheezing in association with viral infections and the more chronic asthma characteristic of older children. As the children in the present study are followed up as part of an ongoing prospective study it should become clear by their outcome whether the evidence supports the view that all childhood wheezers arise from a single population[7] or alternatively, as proposed on theoretical grounds[6] and by indications from a prospective study,[1] that two populations exist which can only be differentiated by the development of atopy with the passage of time.

We are grateful to the National Asthma Campaign for their support of this study.

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Archives of Disease in Childhood 1992; 67: 496–500

Enhanced allergic sensitisation related to parental smoking

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Abstract

The objective of this study was to assess the role of parental smoking in changes, after a four year interval (1983–7), in the prevalence and severity of the atopic state in 166 preadolescent children. Allergy skin prick tests were related to parental smoking habits and their changes during this same interval.

The total number of cigarettes smoked by parents decreased in 56 families while it increased in only 16. Boys had significantly more persistently positive skin tests and changed more frequently from negative to positive. The skin test index did not show significant changes in girls. This index did not change in children of persistent non-smokers or those starting to smoke during this period, while it increased among sons of those that quit smoking and of persistent smokers. This was not only due to those boys who became skin test positive during follow up. When analysis was restricted to 14 boys who had been skin test positive in 1983 and whose parents were persistent smokers, the index increased in eight, remained unchanged in four, and decreased in only two.

This report supports the hypothesis that parental smoking is a factor that, together with specific allergenic exposure, may enhance allergic sensitisation in children.

A significant association has been described between the prevalence of atopy in children (as assessed by skin prick tests to the most frequent allergens) and the smoking habits of their parents.[1 2] This has stimulated new interest in the study of the environmental factors that may enhance atopic expression in predisposed subjects.

Recently a very high correlation has been reported between the incidence of asthma and markers of the atopic state in a large general population sample.[3] If asthma is associated with allergic sensitisation,[3] then avoidance of factors predisposing to atopy during childhood may help prevent asthma and chronic airflow limitation later in life.

When we studied a random sample of 166 children aged 9 years, we showed that the prevalence of atopy was significantly higher in the sons of smoking parents than in the sons of non-smoking parents. We also showed, again in boys, that a prick skin test index, calculated from the combined diameters of the weals elicited by the allergens, was correlated with the total number of cigarettes smoked by their parents. We hypothesised that parental smoking, by increasing the risk of atopy, may increase the risk of asthma, particularly in their sons.[2]

Little is known about longitudinal changes occurring in skin prick test reactivity during the preadolescent years. Barbee *et al* reported that, out of 70 subjects aged 6–14 years, 15 (21·4%) had converted from initial negative to positive after a mean of 8·1 years of follow up, while 27 (38·6%) remained consistently positive, and 28 (40%) remained consistently negative. No subject became skin test negative during this age interval.[4] These investigators also reported that, paradoxically, total IgE concentrations decreased both in consistent atopic and consistent non-atopic subjects in this same age interval.[5] Factors other than the direct genetic control of IgE concentrations may play a significant part in atopic sensitisation during this crucial period of life.

The objective of this present study was to assess the role of parental smoking in changes of prevalence and severity of the atopic state in children originally enrolled at the age of 9 years. For this purpose we recalled, after a four year interval, the group of 166 subjects in whom these relationships had already been studied in 1983.[2] Allergy skin prick tests were repeated and results were related to parental smoking habits during this same interval.

Subjects and methods

Between September and November 1987 the families of all children in three Italian towns in the Viterbo province (Ronciglione, Caprarola, and Carbognano) who were previously studied at the age of 9 years in 1983, were contacted through their junior high school. Eight families had moved to other towns or could not be found. Informed consent was obtained from 142 (72 boys and 70 girls) of the remaining 158 families, a participation rate of 85·5%. There were no significant differences in health status, prevalence of positive skin tests, or parental smoking habits in 1983 between participants and non-participants in the longitudinal study.

A questionnaire, identical to that used in the previous survey, was administered to one parent. Questions on possible changes in smoking habits of each parent were added. To assess the importance of these changes, households were classified into four groups: (i) those in which there was at least one smoking parent both in 1983 and in 1987 ('persistent smokers'); (ii) those in which both parents were non-smokers, both in 1983 and in 1987 ('persistent non-smokers'); (iii) those in which at least one

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Accepted 15 November 1991

parent smoked in 1983 and both parents were non-smokers in 1987 ('quitters'); and (iv) those in which both parents were non-smokers in 1983 and at least one parent was a smoker in 1987 ('starters'). As no difference was found in this sample between the effects of paternal and maternal cigarette smoking on skin test reactivity and bronchial responsiveness in the 1983 survey, no effort was made to differentiate these effects during follow up.[2]

Independently from this questionnaire, each child was interviewed privately by a physician regarding his/her cigarette smoking habits, after assuring the child of the confidential character of the interview. Specifically, children were asked: 'Have you ever tried to smoke cigarettes?'. If they answered affirmatively, they were asked if this had happened 'once or twice', 'seldom', or 'at least once a week'. An additional question asked them to specify the number of cigarettes smoked per week or day.

Allergy skin tests were performed using standard skin prick test methods. Extracts used were the same as those applied in our previous survey, namely house dust mites, *Alternaria tenuis* (fungus), *Aspergillus fumigatus* (fungus), *Poa pratensis* (grass), *Artemisia vulgaris* (compositae), *Parietaria officinalis* (urticaceae), *Olea europea* (olive), milk albumin, egg albumin, and cat dander. These represent the most prevalent allergens in central Italy. Operators were unaware of the results of the skin prick tests in the previous survey. The diameters of the weals elicited by the allergens (minus the diameter produced by the control solution) were summed and a skin test index was created with the following classes: class 0=0 mm, class 1=1–2 mm, class 2=3–4 mm, class 3=5–8 mm, class 4=9–16 mm, and class 5=>16 mm.

In addition, four categories of subjects were described by comparing the results of their skin prick test performed in 1983 and in 1987: persistently positive, persistently negative, conversion from negative to positive, and conversion from positive to negative.

Table 1 Prevalence of smoking among parents in 1983 and in 1987. Results are number (%)

Survey	*Both parents non-smokers*	*Father smokes only*	*Mother smokes only*	*Both parents smokers*	*Total*
1983	39 (27)	55 (39)	13 (9)	35 (25)	142 (100)
1987	53 (37)	51 (36)	12 (9)	26 (18)	142 (100)

Table 2 Changes of skin prick test reactivity between 1983 and 1987 by sex. Results are number (%)

	Skin tests				*Total*
	Persistently positive	*Changed from + to −*	*Changed from − to +*	*Persistently negative*	
Boys	19 (26)	3 (4)	12 (17)	38 (53)	72
Girls	9 (13)	4 (6)	2 (3)	55 (78)	70
Total	28	7	14	93	142

Fisher's exact test, χ^2 test, Wilcoxon's signed ranks test, and Kruskal–Wallis non-parametric analysis of variance were performed using standard Statistical Package for Social Sciences programs.[5]

Results

Table 1 shows the pevalence of current smokers among mothers and fathers of children included in this study, both for the first survey (1983) and for the present survey (1987). The percentage of non-smoking families increased from 27% to 37%. In 29 families at least one parent stopped smoking, while in 11 one parent started to smoke; in 102 there was no change in the number of smoking parents during this four year interval ($p=0·009$ by Wilcoxon's signed ranks test). Moreover, the total number of cigarettes smoked by parents decreased in 56 families while it increased in only 16 ($p<0·0001$).

Table 2 shows the numbers and percentages of boys and girls among subjects whose skin tests were persistently positive, persistently negative, changed from positive to negative, or changed from negative to positive. Boys were significantly more persistently positive (odds ratio=3·1, $p=0·03$, 95% confidence interval (CI) 1·2 to 8·1) and changed more frequently from negative to positive (odds ratio=8·7, $p=0·004$, 95% CI 1·2 to 8·2). The proportion of skin test positive girls went from 18·6% in 1983 to 15·8% in 1987, while that of skin test positive boys went from 30·6% to 43·1% during that same interval. As a consequence, mean (SD) skin test index increased significantly in boys from 0·70 (1·34) to 1·32 (1·79), with $p=0·0003$ by Wilcoxon's signed rank rest; but in girls it only increased from 0·46 (1·07) to 0·59 (1·16), $p=0·03$. Seven children (three boys, four girls) changed from positive to negative, but their mean skin test index was 1·4 in 1983—that is, their geometric mean sum of the weal sizes was only between 2 and 4 mm.

Table 3 shows the relationship between parental smoking in 1987 and changes in the results of skin prick tests by gender. In girls, there was no significant relationship between exposure to parental tobacco smoke and the results of skin prick tests performed in 1987 or changes in skin test reactivity between 1983 and 1987. However, 11/34 (32%) sons of a smoking parent became skin positive during the follow up, compared with 1/16 (6%) sons of non-

Table 3 Relationship between parental smoking habits in 1987 and changes in skin prick tests by gender. Results in number (%)

	Skin tests				*Total*
	Persistently positive	*Changed from + to −*	*Changed from − to +*	*Persistently negative*	
Boys:					
At least one smoking parent	12 (25)	2 (4)	11 (23)	23 (48)	48 (100)
Both parents non-smokers	7 (29)	1 (4)	1 (4)	15 (63)	24 (100)
Girls:					
At least one smoking parent	5 (12)	2 (5)	2 (5)	32 (78)	41 (100)
Both parents non-smokers	4 (14)	2 (7)	0 (0)	23 (79)	29 (100)

smoking parents (p=0·04 by Fisher's exact test).

When the households of the boys were classified into four groups (persistent smokers, persistent non-smokers, quitters, and starters, see methods), the parents were more likely to quit smoking between 1983 and 1987 if their sons were skin test positive in 1983. Altogether 60% (6/10) of boys belonging to families where at least one parent smoked in 1983 and none smoked in 1987 were skin test positive in 1983 compared with 7% (1/14) of atopic boys in families of persistent non-smokers (p=0·007 by Fisher's exact test). To avoid the confounding effect of this preferential quitting of smoking by families of atopic boys, we repeated the analysis after excluding households in which parental smoking habits had changes during the follow up period. None of 13 skin test negative sons of persistent non-smokers became skin test positive during follow up, while 11/33 (33%) sons of persistent smokers became skin test positive during follow up (p=0·01 by Fisher's exact test).

To assess if parental smoking was also associated with an increase in skin test reactivity, the difference between skin test index (STI; expressed in classes, see methods) in 1987 and that in 1983 (delta STI=STI87−STI83) was computed for each subject. In general, mean skin test index did not change in children of persistent non-smoking parents and significantly increased in children whose parents were persistent smokers. This increase was significantly larger in boys than in girls (p=0·04 by Kruskal-Wallis one way analysis of variance, ANOVA).

The skin test index did not change or become negative in girls belonging to households where parents were persistent non-smokers, starters, or quitters. Daughters of persistent smokers had higher mean skin test index than daughters of persistent non-smokers (table 4), but this difference did not reach significance (p=0·15 by ANOVA). Conversely (table 4), the skin test index did not change in sons of persistent non-smokers or starters, while it increased during follow up among sons of quitters and of persistent smokers (p=0·03 by ANOVA). This was not only due to those boys who became skin test positive during follow up; when analysis was restricted to 14 boys who were skin test positive in 1983 and who had parents who were persistent smokers, the skin test index increased in eight, remained unchanged in four, and decreased only in two (p=0·0004 when compared with sons of non-smoking parents).

Forty six children (32%) answered affirmatively to the question 'Have you ever tried to smoke cigarettes?' When asked more detail about these experiences, however, most (n=31, 22%) affirmed that this had happened only 'once or twice', while eight (6%) said they had experienced smoking 'seldom', and seven (5%) acknowledged smoking at least one cigarette a week. Only two children acknowledged smoking one cigarette a day. In this sample, these first experiences with cigarette smoking were not significantly more frequent in children of smoking parents, and the 15 children who smoked 'seldom' or 'at least one cigarette a week' did not as a group have more smoking parents than children who said they had never tried to smoke cigarettes. There was no significant effect of active smoking on prevalence of (or changes in) skin test reactivity. Exclusion of the above mentioned 15 children from the analyses did not change the results.

Table 4 Changes of skin test index during follow up by parental smoking habits and by gender

	Delta skin test index		
	Boys	*Girls*	*Total*
Persistent non-smokers:			
Mean (SD)	0·00 (0·39)	0·00 (0·92)	0·00 (0·74)
No of parents	14	20	34
Starters:			
Mean (SD)	0·00 (0·00)	−1·00 (1·41)	−0·40 (0·89)
No of parents	3	2	5
Quitters:			
Mean (SD)	0·50 (1·58)	−0·11 (0·78)	0·21 (1·27)
No of parents	10	9	19
Persistent smokers:			
Mean (SD)	0·87 (1·36)*	0·30 (0·95)	0·61 (1·21)**
No of parents	45	39	84

*p=0·03 when compared with male children of persistent non-smokers
**p=0·005 when compared with children of persistent non-smokers
Delta skin test index (STI)=STI in 1987 minus STI in 1983

Discussion

The main finding of this longitudinal study is that, between the ages of 9 and 13 years, skin test reactivity to common aeroallergens increases significantly both in frequency and intensity in children, especially in boys, of smoking parents, while it remains unchanged in children of non-smoking parents. If we tested boys and girls separately we found no significant effect of parental smoking upon skin test reactivity in girls. These findings are in agreement with our previous report[2] of an increased prevalence of skin test reactivity to the same aeroallergens in boys but not in girls in a study of this same population sample at the age of 9 years.

It has long been known that atopy runs in families and that this is likely to be due to a genetic predisposition.[6–9] Recent studies have been implied that atopy has a dominant inheritance pattern and that the gene locus is in chromosome 11.[10] However, many environmental factors are known to modulate the phenotypical expression of this allergic predisposition. In children of atopic parents, for example, the development of allergy has been temporally associated with the incidence of viral infections.[11]

Active smoking is known to increase the incidence of allergic sensitisation to occupational exposures in otherwise non-atopic subjects. Zetterstrom *et al* showed that total IgE concentrations increased significantly in rats exposed to tobacco smoke.[12] They also reported that ovalbumin specific IgE increased significantly in smoke exposed rats when ovalbumin was administered by aerosol but not when rats were immunised against this protein by a subcutaneous route.

This present report supports the hypothesis that parental smoking is a factor that, in conjunction with specific allergenic exposure, may enhance allergic sensitisation in children. Some inaccuracy may be introduced by the self reported questionnaire in which each subject has to establish carefully how many cigarettes he smokes. However, our data compare two successive studies in which the same parameters are operating.

It is unlikely that the reported results may be due to other factors. The study subjects belong to a stable rural population on the outskirts of Rome and among whom immigration and emigration are rare. Social status was not significantly different between parents who were smokers or non-smokers, or between persistent smokers, quitters, starters, and 'never smokers', and it is thus not likely to explain our results. It could be argued that active smoking may be more frequent in the sons of smoking parents in this age group and that this could explain our findings. However, we asked children confidentially about their smoking habits and there was no relationship between the responses to this questionnaire and changes in skin test reactivity. In addition, we had previously reported similar gender specificity in the effect of parental smoking when these children were 9 years old,[2] an age at which it is unlikely that children in our social setting could have started smoking cigarettes. Finally, Burrows *et al* reported that non-atopic subjects tended to smoke cigarettes more often than atopic subjects, while the latter tended not to start smoking and to give it up if they did begin.[13] In other words, current smokers had lower atopy rates than ex-smokers and never smokers.[13] This is opposite to our finding that sons of smoking parents tended to have higher skin test reactivity than sons of non-smoking parents.

No study has been reported that relates changes in skin test reactivity in children to parental smoking habits, and only one has dealt with the issue of longitudinal changes in skin test reactivity in children. Barbee *et al* reported that skin test reactivity increased significantly both in boys and girls between 6 and 14 and only reached a peak between 20 and 45 years of age.[4] Our studies would suggest, however, that skin test reactivity is stable between 9 and 13 years of age in girls and in the sons of non-smoking parents. In these groups, very few skin test positive subjects became skin test negative, and in those who did, the size of the initial weal was small (geometric mean of <2 mm) and perhaps clinically irrelevant.[5] In these same groups, very few subjects became skin test positive (see table 3). The situation was very different, however, for the sons of smoking parents. Almost one in four of these children became skin test positive during follow up. Barbee *et al* did not report on the influence of parental smoking or other environmental stimuli on their subjects, and it is thus not possible to compare their findings with ours.[4]

The mechanism by which environmental tobacco smoke enhances sensitisation to aero-allergens is unknown. The studies by Zetterstrom *et al* in rats suggest that a direct contact between the allergen and the bronchial mucosa is necessary for this increased sensitisation to occur.[12] This would support the hypothesis that a disruption of the bronchial epithelium by tobacco smoke with increased permeability to antigens may be involved.[14] It is also possible, however, that the disruption of the epithelium seen in animal models of tobacco smoke inhalation may be the consequence of an inflammatory process occurring in the mucosa, which may also alter the mechanisms by which the aero-allergens are handled and presented to immunocompetent cells in the lung. Active cigarette smoke has also been found to be associated with changes in T lymphocyte function[15] and it is possible that these changes may alter the complex immunological mechanisms involved in the regulation of IgE production.[16] Experimental studies are needed to determine the relative importance of these possible mechanisms in determining an increase in allergy skin test reactivity in children of smoking parents.

As in our previous reports, we found that the association between parental smoking and allergy skin test reactivity was much more evident in boys.[2 17] We also found that boys were twice as likely to be skin test positive than girls; this was independent of parental smoking habits (table 3). One possible explanation is that our data cover a small segment of life span in which a difference in age of atopic maturation could cause differences between sexes similar to those we have found. Otherwise, as the gender distribution of atopy does not seem to be directly determined by heredity,[18] environmental factors may play a significant part in determining the difference in prevalence of atopy between genders. Boys may be more susceptible to environmental noxious stimuli and thus more prone to become sensitised to aeroallergens when their parents smoke.

A significantly higher proportion of smoking parents whose sons were skin test positive in 1983 stopped smoking between 1983 and 1987 when compared with parents of skin test negative children. This was probably due to the fact that we considered it unethical not to inform parents of the results of our previous study and these results may have induced some parents of atopic children to quit smoking.[2] It is also possible that some of these parents who quitted smoking may have been atopic themselves and thus may have been more likely both to quit smoking[13] and to have children predisposed to develop skin test reactivity. This may explain at least in part the increase in skin test index among sons of quitters (see table 4). An alternative explanation is also possible, however; early exposure (at or before the age of 9) to cigarette smoke may be more important than that occurring between 9 and 13 years in determining allergic sensitisation. Longitudinal studies including parental skin test reactivity are necessary to elucidate this issue.

This study was supported in part by grants from Progetto Finalizzato Medicina Preventiva, Subprogetto Medicina Perinatale, Consiglio Nazioanale delle Ricerche

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Human herpesvirus-6

Unless another one has been discovered fairly recently, there are six known human herpesviruses: herpes simplex viruses 1 and 2, cytomegalovirus, varicella zoster virus, Epstein-Barr virus, and human herpesvirus-6 (HHV-6). The latter was identified as the cause of exanthem subitum (roseola infantum) by Japanese workers in 1988.[1] Infection with HHV-6 is almost universal in young children and between 80 and 100% of young adults around the world are seropositive, but antibody titres decline after the age of 40.[2] A very high percentage of adults (more than 85% in this Californian series[2]) shed the virus in saliva and this is the presumed vehicle of infection. Exanthem subitum is, of course, usually benign but infant fatalities have been described, in Japan from fulminant hepatitis[3] and in China from haemophagocytic syndrome.[4]

A recent report, again from Japan, gives details of the virological findings in 89 infants with exanthem subitum (Yoshizo Asano and colleagues, *Journal of Pediatrics* 1991;**118**:891–5). They showed that children who had prolonged fever (four days or more) had significantly greater viraemia than those with a short fever (three days or less).

For a long time it has been suggested that exanthem subitum might be an important cause of febrile convulsions. Now that the virus is identified we can presumably look forward to early clarification of this relationship.

The Japanese have contributed much to modern medicine. A history of the contribution would be well worth reading.

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Archives of Disease in Childhood 1992; 67: 501–505

Middle aortic syndrome: clinical and radiological findings

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Accepted 11 December 1991

Abstract

Eight patients with the middle aortic syndrome are described. They were aged 2 months to 14 years at diagnosis; follow up was one to 11 years. Clinical presentations included asymptomatic hypertension (n=5), severe headache, nose bleed, and chest pain (n=1), and cardiac failure (n=1). All had severe hypertension requiring multiple drug treatment. Diminished peripheral pulses were not helpful in the diagnosis, which is made on aortography. Associated clinical findings were Williams' syndrome (n=3) and appreciable eosinophilia (n=3). The differential diagnosis includes Takayasu's arteritis, fibromuscular dysplasia, and neurofibromatosis. Blood pressure was adequately controlled by medical treatment in six patients. Surgical angioplasty was performed in two. One patient remained normotensive without drug treatment 21 months after operation; the other died of sepsis and uncontrollable haemorrhage in the postoperative period. Medical treatment is satisfactory in most cases: surgery should be reserved for those in whom blood pressure cannot be controlled without unacceptable side effects of drug treatment. Although rare, the middle aortic syndrome should be considered in the differential diagnosis of hypertension when commoner causes have been excluded. Aortography is necessary for diagnosis.

The middle aortic syndrome (MAS) is an uncommon condition and is characterised by severe narrowing of the abdominal aorta with involvement of the renal and visceral branches. It was first described by Sen *et al* in 1963.[1] The disease is an important cause of hypertension in children and young adults, and is associated with a high morbidity and mortality.[2] Several reports of the results of surgical and percutaneous transluminal angioplasty have appeared.[3–6] It is evident from these that surgery is difficult and not always feasible and that transluminal angioplasty is usually ineffective. The treatment of choice is medical control of blood pressure in most patients, especially the very young.

The purpose of this paper is to review the clinical features, angiographic findings, associated diseases, and management in eight children with MAS diagnosed at Guy's Hospital between 1975 and 1988.

Patients

DEMOGRAPHIC FEATURES

Six of the eight patients included in the report were boys and two girls. The age range at diagnosis was 2 months to 14 years (mean 8·3 years). Five were white, two were Pakistani, and one was Egyptian. The perinatal history was unremarkable in all cases. There was no known history of an affected relative in any of the patients' families.

CLINICAL FINDINGS

There were no symptoms in five cases, hypertension having been discovered because blood

Table 1 Clinical features in MAS

Case No	*Age at diagnosis (years)*	*Sex*	*Race/ nationality*	*Blood pressure at diagnosis (mm Hg)*	*Other diagnoses*	*Treatment*	*Follow up (years)*	*Remarks*
1	0·2	F	Egyptian	120/80	Multiple congenital abnormalities with developmental delay	Captopril, frusemide, minoxidil	1 1	TORCH screen and karyotype normal. Normotensive at follow up
2	1·3	M	White	180/?	Appreciable eosinophilia	Frusemide, spironolactone	2·0	Hirsutism
3	6 8	F	White	190/130	—	Surgical angioplasty and autotransplant	1·8	Normotensive at follow up
4	6·8	M	White	170/130	Appreciable eosinophilia	Captopril, frusemide, amiloride, propranolol, nifedipine, prazosin	11·0	Hirsutism Hypertensive crisis after first aortogram Repeat aortogram. no change at 10 years
5	11·1	M	White	160/?	Williams' syndrome, supravalvular aortic stenosis, appreciable eosinophilia	Frusemide, amiloride, atenolol	1·5	—
6	12 4	M	Pakistani	Not recorded	Williams' syndrome, pulmonary stenosis, developmental delay	Surgical angioplasty and autotransplant	1 week	Postoperative death (sepsis, bleeding)
7	13·8	M	Pakistani	220/150	Tuberculin test positive (no history of BCG)	Captopril, frusemide, atenolol, nifedipine, minoxidil	3·2	Extensive extra-abdominal arterial disease
8	14 2	M	White	160/90	Williams' syndrome hyperuricaemia? cause, developmental delay	Bendrofluazide, atenolol	0	Lost to follow up

pressure was measured for incidental reasons. One patient presented with nose bleed, severe headache, and chest pain and another with cardiac failure. The clinical record was incomplete in the eighth case. Examination revealed severe hypertension in all, an ejection systolic murmur at the left sternal border in four, weak peripheral pulses in two, abdominal bruits in five, bilateral carotid and orbital bruits in one, and hypertensive retinopathy in two (table 1). Renal function was normal in five, impaired in one, and not recorded in two. The erythrocyte sedimentation rate (ESR) was normal in six and not recorded in two. Antinuclear antibodies were not detected in the five patients tested. Three patients had Williams' syndrome; two of these also had supravalvular aortic stenosis not requiring surgical treatment. The hyperuricaemia observed in the third patient with Williams' syndrome is unexplained: it was present before he was given bendrofluazide. Three had persistent eosinophilia, ranging from 780 to 1870×10^6/litre. One (case 7) had a positive Mantoux test without a history of BCG immunisation, the significance of which is unknown: there was no other evidence of tuberculosis. Case one had multiple congenital abnormalities: single umbilical artery, severe growth and developmental delay, flexion deformities of all limbs, microphthalmia with severe visual impairment, corneal clouding, sensorineural deafness, and microcephaly with dilated cerebral ventricles and cortical atrophy. Renal function at latest follow up was normal in three patients (cases 2, 3, and 5) with plasma creatinine concentration 70, 54, and 83 μmol/l respectively, reduced in cases 4 and 7 (113 and 143 μmol/l), both of whom were receiving captopril, and unavailable in cases 1 and 8 (records lost) and case 6 (died).

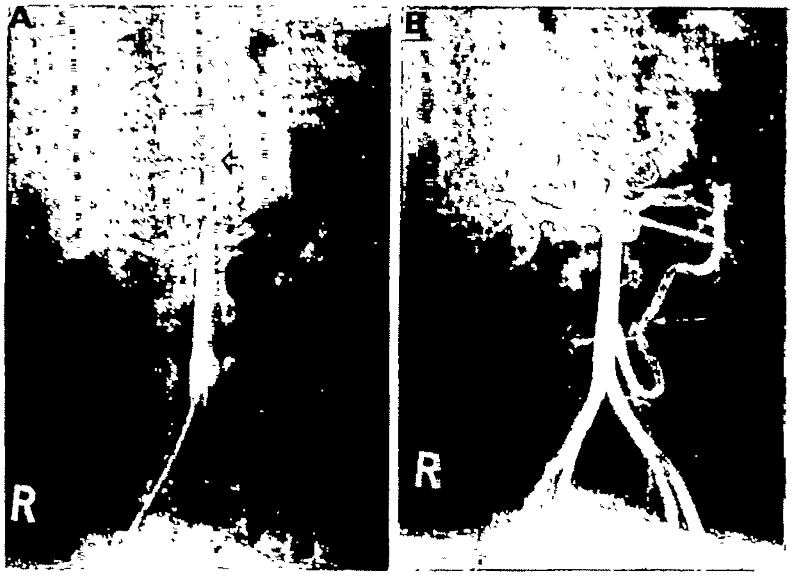

Figure 1 Case 4 aged 6. (A) There is severe narrowing of the abdominal aorta and stenosis of both the origin of the coeliac (open arrow) and the superior mesenteric arteries. (B) There is also an enlarged collateral from the inferior mesenteric artery (the 'wandering artery of Drummond') (white arrow).

RADIOLOGICAL FINDINGS

Aortography was performed via the percutaneous femoral approach in all patients. Originally, studies were with film but more recently, digital angiography has been used. Oblique views were obtained as necessary to demonstrate the origins of the renal arteries and mesenteric vessels. Follow up arteriograms were obtained in two patients (time intervals: case 2 of one year and case 4 of 10 years). Three patients additionally had examinations of the aortic arch. All patients had smooth segmental narrowing of the abdominal aorta over a variable distance (table 2). In five patients, this narrowing extended above the renal arteries. All eight patients had involvement of the renal arteries, bilaterally in seven. The superior mesenteric and coeliac arteries were affected in five patients. The inferior mesenteric artery was spared in all

Table 2 Radiological findings in MAS

Case No	*Aortic arch*	*Abdominal aorta*	*Renal*	*Coeliac*	*Superior mesenteric*	*Inferior mesenteric*	*External iliac*	*Repeat study*
1	Not studied	Very narrow from diaphragm to bifurcation	Narrowed	Not seen	Narrowed	Not seen	Not seen	Not done
2	Abnormal vertebrals with extensive collaterals	Diffusely narrowed at level of renal arteries	2R.both stenosed, 2L:normal	Normal	Normal	Normal	L·occluded, R.narrowed	Yes
3	Normal	Irregular narrowing from diaphragm to just above origin of superior mesenteric artery	Both stenosed with poststenotic dilatation	Occluded	Occluded	Enlarged	Normal	Not done
4	Normal	Narrowed T11-L2	3L all narrowed, 1R narrowed	Narrowed origin	Narrowed origin	Enlarged	Normal	Yes
5	Not studied	Diffuse tubular narrowing of whole abdominal aorta, extending supra-renally	Bilateral proximal stenosis	Normal	Normal	Normal	Normal	Not done
6	Not studied	Narrowed T12-L2	Narrowed origins	Severe stenosis of origin with poststenotic dilatation	Severe stenosis of origin	Enlarged	Normal	Not done
7	Stenosis of right subclavian	Dilated segment above slight narrowing at level of renal arteries	2R both narrowed, 2L:one normal, one occluded, intrarenal stenoses	Occluded	Occluded	Enlarged	Normal	Not done
8	Not studied	Diffuse tubular narrowing at level of renal arteries	2L:larger stenosed, smaller normal, 1R.proximal stenosis with poststenotic dilatation	Normal	Normal	Normal	Normal	Not done

R=right, L=left.

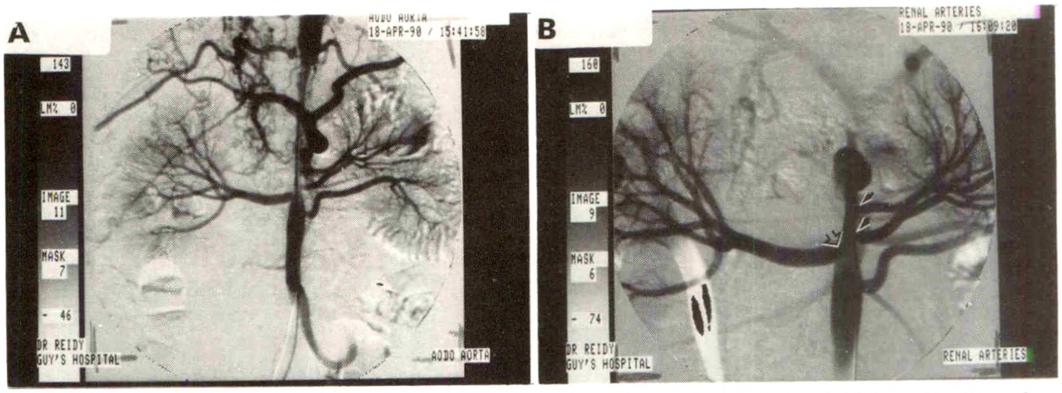

Figure 2 Case 4 aged 16. (A) There has been no significant change in appearance. (B) The stenosis of the proximal two of the three left renal arteries at their origin (solid arrows) and the slight narrowing of the origin of the single right renal artery (open arrow) are more clearly seen.

cases. Only one patient (case 2) had an abnormality of the iliac arteries (table 2): he also had abnormal vertebral arteries with extensive collateral formation and a subsequent angiogram a year later showed some progression of his iliac artery lesions. In contrast, the other patient studied twice (case 4) showed no change to his extensive disease in the 10 years that separated the studies (figs 1 and 2). Arch aortography was normal in case 3 but showed narrowing of the right subclavian artery in case 7. The appearances on abdominal aortography were almost identical in cases 3 and 6, as shown in figs 3 and 4 respectively. A hypertensive crisis occurred in one patient (case 4) as a complication of arteriography and was controlled only with great difficulty. No other complications were seen.

Treatment

Percutaneous transluminal angioplasty was not attempted in any patient in the series. Two patients were operated on. One (case 3) was successfully treated at 6·8 years of age with a thoracic aorta to aortic bifurcation Dacron bypass graft and bilateral autotransplantation of both kidneys. She remains normotensive 21 months after operation. The other (case 6), aged 12·4 years at the time of operation, died of Gram negative sepsis and massive bleeding five days after having a left renal autotransplant and a right iliorenal saphenous vein bypass graft. Surgery was not attempted in the other six patients because their lesions were considered technically inoperable and/or because medical control of hypertension was satisfactory. Medical treatment with combinations of two to six antihypertensive drugs was given to seven patients with moderate to good control of the blood pressure. The antihypertensive policy used varied somewhat over the period of the

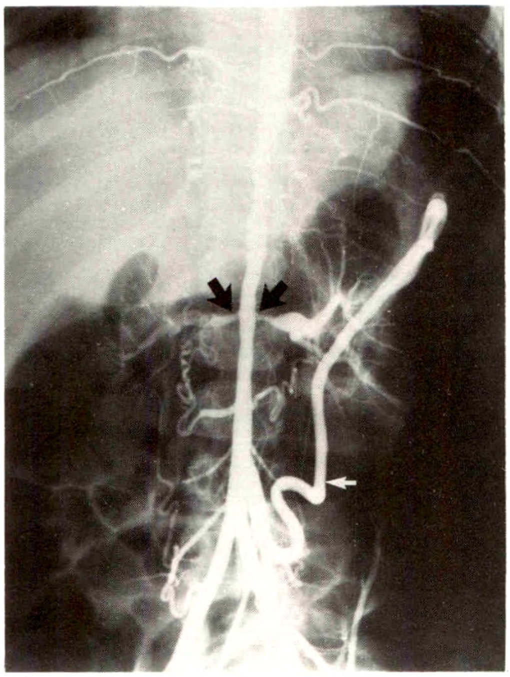

Figure 3 Case 3 aged 6. The abdominal aorta is severely narrowed. The coeliac and superior mesenteric arteries have not filled. There is enlargement of intercostal arteries and collaterals from the inferior mesenteric artery (white arrow). There is also stenosis of the origin of both renal arteries with poststenotic dilatation (black arrows).

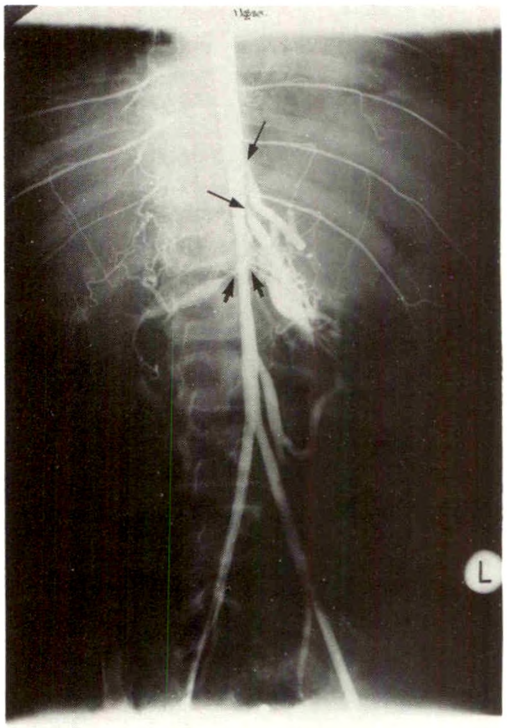

Figure 4 Case 6 aged 12. The appearances are almost indistinguishable from those of case 3 (fig 3). There is again narrowing of the abdominal aorta. The origins of both renal arteries are stenosed with poststenotic dilatation (thick arrows). There is stenosis of the origins of the coeliac and superior mesenteric vessels (thin arrows) with collateral formation from the inferior mesenteric artery.

study, but in general a diuretic was prescribed first, and if satisfactory control was not achieved with the maximum recommended dose other drugs were added, usually in the following order: first a β-adrenergic blocker, second a vasodilator, and finally an angiotensin converting enzyme inhibitor. The combinations and dosages varied within each patient over time: the drugs listed in table 1 are those prescribed during the most difficult period of blood pressure control in each patient. The mean period of follow up was 40 months (range 13–127 months). After 13 months follow up, one patient gradually became normotensive without antihypertensive drug treatment. Complications of drug treatment included minoxidil induced hirsutism in two and reversible, dose dependent, captopril induced impairment of renal function in one.

Discussion

MAS is an uncommon condition that can cause severe hypertension with its attendant risk of life threatening complications. The disease should be suspected in any young, severely hypertensive patient in whom renal and endocrine causes of hypertension have been excluded by routine investigations, and especially if abdominal bruits, eosinophilia of unknown origin, or Williams' syndrome are present. Poor volume peripheral pulses, although a pointer to the diagnosis, were found in only two of our patients and they cannot be differentiated from the findings in coarctation of the aortic arch which is more common in this age group.[7 8] Systemic hypertension secondary to diffuse narrowing of the abdominal aorta has been reported previously in patients with Williams' syndrome,[9 10] and the findings in our patients suggest that this association occurs more commonly than would be predicted by chance alone. Appreciable eosinophilia has not been reported before in MAS, and might suggest an allergic or immunological aetiology.

The differential diagnosis includes other important causes of renovascular hypertension in children such as Takayasu's arteritis, fibromuscular dysplasia, neurofibromatosis, and mucopolysaccharidoses. Patients with neurofibromatosis may have stenosis of the abdominal aorta and its branches including the renal arteries but the disease does not affect the aorta and the lesions differ angiographically from those of MAS,[11] as do those of fibromuscular hyperplasia.[12–14] The differentiation between MAS and Takayasu's arteritis may be difficult: clear criteria for separating the two do not exist. Nevertheless, it is worthwhile attempting to make the distinction as anti-inflammatory drugs may be useful in some patients with Takayasu's disease. The latter condition occurs primarily in young women with associated rheumatic complaints including arthritis, myalgia, pleuritis, pericarditis, fever and rash, none of which was present in any of our patients. The ESR is usually raised. A mixed type of segmental involvement of arteries is often present and the disease is very uncommon in non-oriental populations.[2 15 16] An arteriopathy very similar to that of MAS has recently been described in mucopolysaccharidoses 1 H (Hurler's syndrome) and 1 S (Scheie's syndrome).[17] None of our cases had features suggestive of any form of mucopolysaccharide storage disorder.

Aortography is the only investigation diagnostic for MAS. From our own experience and that of others, it is recommended that aortography should be performed in all severely hypertensive patients in whom the diagnosis has not been established from initial renal imaging (ultrasonography, radionuclide scintigraphy, and excretory urography), plasma renin activity, plasma aldosterone, and urine and plasma catecholamine estimation.[18 19] Meticulous blood pressure control must be maintained during and after arteriography: a hypertensive emergency occurred in one of our patients.

The choice of antihypertensive drugs is not different from that conventionally used in renovascular and other severe forms of hypertension. Most patients in the present series responded well to captopril combined with a diuretic and/or a vasodilator and/or a β-adrenergic blocker. Renal function should be closely monitored in all patients receiving an inhibitor of angiotensin converting enzyme.

The indications for surgery in MAS have not been established. Surgical mortality is high due to the extensive nature of the vascular abnormality and the difficulty in fashioning an appropriate graft. Percutaneous transluminal angioplasty has not been reported to be followed by long term success in MAS.[2] Most of our patients have done well on medical treatment alone. In general, we recommend that surgery be reserved for those in whom medical control of blood pressure is unsatisfactory or associated with intolerable side effects, and in whom the disease is judged to be amenable to surgical correction without an unacceptable level of operative risk.

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Co-trimoxazole and life in the raw

No matter how hard their lives may seem people have, in the words of Peter Medawar, 'a very decided preference'[1] in favour of life for themselves and those they love. In the Jumla district of western Nepal life, it seems, is about as tough as it can get. It is a mountainous district with about 80 000 people living at a height of 8 or 9000 feet in a cold, dry climate with no roads, poor housing, low literacy, inadequate food, no routine child health services, and nearly 20% of children dying in infancy. Nevertheless, despite an endemic fatalism about child deaths, one of the striking findings of a recent study (Mrigendra Raj Pandey and colleagues, *Lancet* 1991;**338**:993–7) was that mothers quickly learned to recognise pneumonia and bring their children for treatment.

For every 1000 people one was chosen to be the community health worker and that person was given nine days training, the aim being to teach them to recognise pneumonia in children under the age of 5 years and to treat it with a five day course of co-trimoxazole. The health workers travelled around their villages visiting families with young children every two weeks and actively seeking out cases of pneumonia diagnosed on the basis of tachypnoea and chest indrawing. In the first year of the study only 15% of cases were actively referred by the parents to the health worker but by the third year the proportion was 56%. Pneumonia and diarrhoea accounted for over 60% of deaths in children less than 5 years old with pneumonia predominating under 6 months and diarrhoea after that.

The study lasted for three years and during that time the overall relative risk of death from all causes compared with that before the introduction of the treatment scheme fell from 0·87 (95% confidence interval 0·73 to 1·03) in the first year to 0·72 (0·63 to 0·82) in the third. The relative risk of death from pneumonia was 0·88 (0·59 to 1·32) in the first year of the study and 0·70 (0·50 to 0·97) in the third and from diarrhoea it was 0·81 (0·62 to 1·07) in the first year and 0·64 (0·52 to 0·77) in the third. The health workers were given no training in the treatment of diarrhoea and the improvement in diarrhoeal death rate was attributed to better overall health and nutrition of the children consequent upon the treatment of pneumonia. By far the greatest reduction in mortality was in the second six months of life. In that age group the relative risk of death from all causes was 0·68 (0·43 to 1·08) in the first year of the study and 0·36 (0·24 to 0·55) in the third. In children between 1 and 5 years the effect was relatively disappointing (relative risk 1·02 (0·76 to 1·37) in year 1 and 0·89 (0·73 to 1·09) in year 3).

This study shows that uneducated local people can be taught to recognise and treat pneumonia in young children with a subsequent fall in infant mortality and the financial cost was small (less than US$4 per child per year). Mothers soon learn to suspect pneumonia and respond to the provision of a service. Presumably the next step will be to teach them how to manage diarrhoea.

ARCHIVIST

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[1] Medawar J. *A very decided preference: life with Peter Medawar*. Oxford: Oxford University Press, 1991.

Archives of Disease in Childhood 1992; **67**: 506–508

Vesicoureteric reflux and renal scars in asymptomatic siblings of children with reflux

Rajko B Kenda, Jurij J Fettich

Abstract

The purpose of the study was to determine the incidence of vesicoureteric reflux (VUR), renal scars and hypertension in asymptomatic siblings of children with VUR. The study comprised 105 siblings of patients with VUR. Their age ranged from 4 months to 6·3 years. All had a direct radionuclide voiding cystography (DRVC) performed, and VUR was detected in 47 of 105 (45%). High grade VUR in the first year of life had an incidence of 50% compared with a 9% incidence in siblings older than 2 years, while only one of the 27 siblings with a low VUR grade was younger than 1 year. In 43 of 47 siblings with VUR, a technetium-99m dimercaptosuccinic acid (^{99m}Tc-DMSA) scan was performed and renal scars were found in 10, which presents 23% of siblings with VUR who were scanned and 10% of all siblings studied. One child had hypertension. Identifying VUR among asymptomatic siblings could possibly prevent renal damage and its consequences. Thus, the predictive value of positive family history alone in identifying VUR was 45% while 23% of siblings had renal scars. This incidence justifies the routine investigation of asymptomatic siblings, by using DRVC at an early stage.

Vesicoureteric reflux (VUR) is the most common abnormality detected in children with urinary tract infection (UTI). According to different authors, it is present in 22% to 52% of the children studied.[1–5] On the other hand, the incidence has been estimated to be 1% to 2% in the general population.[6] The rationale of detecting VUR is that by close follow up and/or either surgical or conservative treatment, the risk of renal damage (scarring) and its consequences due to the VUR itself, or to the VUR with associated UTI may be minimised.

The incidence of VUR among siblings (even asymptomatic) of children with known VUR is as high as 45%.[7–11] However, it was not until direct radionuclide voiding cystography (DRVC) with its low radiation exposure was routinely used that VUR detection in siblings became a more widely accepted procedure. Because VUR is normally detected after the UTI, little is known about the natural history of sterile VUR in children and there has not been sufficient data regarding their renal status (scars, hypertension) to recommend screening for VUR routinely. It is known from experimental studies in animals that high pressure reflux can produce renal damage.[12–13]

The purpose of this study was to determine the incidence of VUR in asymptomatic siblings under the age of 6 of patients with VUR and to determine the incidence of renal scars and hypertension in asymptomatic siblings with proved VUR. The results might justify a recommendation to look for VUR in young siblings.

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Accepted 17 December 1991

Patients and methods

One hundred and five siblings of patients with known VUR were admitted to the study from July 1987 to June 1991 inclusive. In 90 families one sibling was evaluated. Two siblings were studied in six families and three in one family. There were 56 (53%) boys and 49 (47%) girls. The age of the siblings ranged from 4 months to 6·3 years (mean age 3·3 years). Fourteen (13%) children were younger than 1 year, 24 (23%) were between 1 and 2 years, while 67 (64%) were older than 2 years. They all had a negative history of UTI and, at the time of admission, they were all free of symptoms.

All children had a DRVC performed and VUR was found in 47 (only a 4 month old boy had a *x* ray voiding cystogram instead of DRVC). Of 47 children with VUR, 43 also had technetium-99m dimercaptosuccinic acid (^{99m}Tc-DMSA) scintigraphy done (in four patients with VUR grade 1 parental permission for DMSA scintigraphy could not be obtained).

The results were reviewed by two independent observers. In cases where there was disagreement, a consensus was reached.

For statistical analyses the χ^2, Student's *t* test, Jonckheere-Terpstra test, and linear by linear association test (StatXact software by Cytel Software Company) were used.

TECHNIQUE OF DIRECT VOIDING RADIONUCLIDE CYSTOGRAPHY

Children were catheterised under aseptic conditions. ^{99m}Tc as sodium pertechnetate was added to sterile isotonic saline in concentrations of 40–80 MBq/l. The bladder was slowly filled with the radiotracer solution under hydrostatic pressure (40–60 cm H_2O). When bladder capacity was reached, or when the child showed the urge to void, the catheter was removed, and the voiding usually began within a short period of time. Since 1990 a cyclic DRVC (filling the bladder and having the infant void around the catheter two or three times) has been used instead of conventional DRVC to increase the accuracy of the procedure. A computerised gamma camera (General Electric Maxi Camera 300, computer Digital PDP 11/34) was used to allow simultaneous visualisation of the radiotracer and to record data at a rate of 1 frame/5 seconds. Data were reviewed with image enhancement by decreasing the upper threshold to 20–30% of maximal radioactivity in the bladder.

All children received co-trimoxazole (Bactrim) 6 mg/kg divided into two doses for three days to prevent UTI after catheterisation.

VUR was classified as unilateral or bilateral. According to its extent it was graded as: VUR 1, radiotracer reaching the ureter only; VUR 2, radiotracer reaching the pelvis; and VUR 3, radiotracer reaching the pelvis, which seemed dilated.

TECHNIQUE OF ^{99m}Tc-DMSA SCINTIGRAPHY

DMSA scintigraphy was performed two hours after the injection of ^{99m}Tc-DMSA. The dose was adjusted for the child's height and weight. One posterior and two posterior oblique images containing 300 000 counts each were obtained with a gamma camera (Siemens Basicam ZLC Digitrac 75) and a low energy all purpose collimator, using an appropriate zoom. The relative contribution of each kidney to the global renal function was calculated using a computer image in posterior projection. DMSA scans were considered to be abnormal if there were focal or generalised scars, or if unilateral function was less than 45% of total glomerular filtration.

Results

Comparing index children and siblings, no significant difference was found in terms of sex ratio (p=0·4), nor was such a difference found between the sex of index children and VUR grade of siblings (p=0·4). There was no significant association between VUR grades of index children and VUR grades of siblings when compared as a whole group (p=0·5). However, in siblings under 1 year of age, the Jonckheere-Terpstra test and linear by linear association test showed significant (p=0·04) positive relationship between VUR grades of index children and VUR grades of siblings, implying that index children with higher grade VUR also had siblings with higher grade VUR. We found that where index children had VUR grade 2 or 3, six of eight siblings under 1 year of age, also had VUR grade 2 or 3.

VUR was detected in 47 (45%) of 105 siblings. It was bilateral in 25 and unilateral in 22 of the patients, thus making 72 refluxing units. The grades of VUR were distributed as follows: 42 (58%) were grade 1, 24 (33%) were grade 2, and six (8%) VUR were grade 3. There was no significant difference between groups of siblings without VUR and those with VUR grade 1, 2, or 3 in terms of sex ratio (p=0·7), but a significant difference (p=0·0001) was found in terms of age (table). The mean age of the children with VUR grade 2 and 3 was 24 months, compared with the mean age of 49 months in those children with grade 1 VUR, and 39 months in children without VUR. High grade VUR (grade 2 and 3) had an incidence of 50% (7/14) in the first year of age, compared with a 9% (6/67) incidence in siblings older than 2 years. On the other hand, only one of the 27 siblings with VUR grade 1 was younger than 1 year.

Distribution of VUR grades 1 to 3 according to age of 47 children with VUR among 105 asymptomatic siblings (in cases of bilateral VUR of different grades, the higher grade was considered). Figures are cases and percentage within each age group

Age (months)	*VUR grade*			
	0	*1*	*2/3*	*Total*
0–12	6 (43)	1 (7)	7 (50)	14 (100)
13–24	12 (50)	5 (21)	7 (29)	24 (100)
25–76	40 (60)	21 (31)	6 (9)	67 (100)
Total	58 (55)	27 (26)	20 (19)	105 (100)

In 43 of 47 siblings with proved VUR, ^{99m}Tc-DMSA was performed and focal defects suggestive of renal scarring were found in 10 cases, which presents 23% of siblings with VUR who were scanned and 10% of all siblings in the study. However, in all cases unilateral renal function was more than 44% of total glomerular filtration. Comparing siblings with VUR and renal scars and those with VUR without scars, no significant difference between the two groups was found in terms of age (p=0·2) and grade of VUR (p=0·6). Significant difference (p=0·02) was noted in terms of sex ratio. Nine siblings with scars were girls and only one was a boy.

In one 9 month old male sibling, in addition to the right VUR, grade 2, a left side kidney agenesis was also discovered. Raised blood pressure was found in one 32 month old boy with bilateral VUR, grade 2, and scars in the upper left pole.

Discussion

The study indicated that the incidence of VUR in general, and of VUR grades 2 and 3 in particular, was much higher in siblings younger than 1 year, than in older siblings, which correlates with the well known fact that VUR tends to disappear with age.

The rationale of detecting VUR in siblings lies in the fact that children with VUR are more prone to pyelonephritis and to develop renal scars than do children without VUR. Besides, it is of considerable interest that most reflux associated renal scars are already present when the patient is first investigated. This suggests that the development of irreversible renal scarring within one week after the introduction of *Escherichia coli* into the bladder of refluxing piglets, as shown by Ransley and Risdon,[14] may also be true in humans. It also indicates the need for more prompt diagnosis and vigorous treatment of the first UTI, as already suggested by many authors.[15–17] It has been widely accepted that renal scarring tends to develop mainly in infants and young children, and that new scars or progression of previous scars rarely occur after the age of 5 years. Recently there is growing evidence that this may not be so, and that the severity of VUR, the frequency of UTI and abnormal bladder function are the main contributing factors.[18] It might be hoped that close follow up and/or either surgical or conservative treatment might reduce the risk of renal scarring in asymptomatic siblings found on the basis of family history to have VUR as most of them will not yet have suffered a symptomatic UTI. However promising, this presumption has not yet been proved.

DRVC is a highly sensitive method and exposes the patient to much less radiation than the *x* ray voiding cystography.[11 19] We believe that the benefit of DRVC in detecting VUR in asymptomatic siblings outweighs the invasiveness of the procedure. We also believe that if screening is to be recommended, DRVC should be the procedure of the first choice. It is the VUR we are looking for, and ultrasound, intravenous urography, or DMSA scintigraphy could only identify children, to whom damage—at least to a certain extent—has already been done. Ten per cent of siblings in this study were found to have renal scars. They do not seem to be of any clinical significance yet, except in one of the 10 children with renal scarring, who has already been shown to have hypertension. Before a more conclusive decision is reached regarding the rationale of screening asymptomatic siblings of patients with VUR, a long term follow up should be done to watch the progress of scars and the development of hypertension in this group and compare it with the findings in children found to have VUR after bacteriologically proved UTI.

It is not clear up to what age the asymptomatic siblings of index children with VUR should be investigated. Van den Abbeele *et al* recommend 10 years as the limit, beyond which siblings should be screened with DRVC, while with older siblings ultrasonography of the kidneys should be done.[10] Noe and Jerkins studied 287 siblings of 221 index patients with VUR and found a 32% incidence of reflux in siblings. However, siblings younger than 18 months had a much higher incidence of reflux than did the older siblings. They recommend a screening voiding cystogram, preferably with radionuclide, for siblings younger than 5 years of age.[20] Their data correlate with ours, where the highest incidence of high grade VUR was seen in children under 2 years of age. On the other hand, a certain number of refluxes of grade 1 (which in our study were discovered mostly in the older children), would have probably been of higher grade if the siblings had been investigated at an earlier age. Aggarwal and Verrier Jones report 33 asymptomatic children with a family history of reflux nephropathy or VUR in first degree relatives.[21] Fifteen (45%) showed some abnormality of the renal tract on ultrasound or micturating cystourethrography, or both, and 12 of them were under 2 years of age.

Based upon present data we believe that the age limit of siblings to whom the DRVC should be done could be lower than 10 years of age as recommended by Van den Abbeele *et al*,[10] but not lower than 2 years. Currently it is our practice to screen with DRVC all preschool siblings of the index child, while older siblings have renal ultrasonography. In addition, parents of a child with VUR are instructed that a newborn sibling should be screened as soon as possible. This procedure is also likely to be justified for children of parents with reflux nephropathy.

In conclusion, identifying children with VUR among asymptomatic siblings could possibly prevent renal damage and its consequences. The predictive value of positive family history alone in identifying VUR in our study was 45%, and 23% of siblings with VUR were found to have renal scars. This appears high enough to justify the routine investigation of asymptomatic siblings of children with VUR, by using DRVC at an early age.

We wish to thank Janez Stare MSc for help with statistical analysis and Linda Cimperman for assistance in the preparation of the manuscript; Tone Žakelj and Ignac Zidar provided technical assistance. The study was financially supported by the Ministry for Research and Technology (grant: URP: C3-0561-363).

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Archives of Disease in Childhood 1992, 67: 509–512

Vulvovaginitis: causes and management

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Accepted 4 December 1991

Abstract

Over a period of 33 months in a paediatric accident and emergency department, the clinical pattern and possible causes of vulvovaginitis were studied prospectively in 200 girls presenting with genital discharge, irritation, pain, or redness. The major causes were poor hygiene and threadworms. The suspicion of sexual abuse arose in a few girls but no organisms of sexually transmitted disease were found. Urinary symptoms were common but only 20 patients had a significant bacteriuria and 40 had sterile pyuria. Specific skin problems occurred in 28 cases.

Simple measures to improve hygiene and treatment of threadworms gave effective relief. Genital irritation caused urinary symptoms with no clinical evidence of infection, and it is advised that antibiotic treatment should await urine culture. Specific skin problems require help from a dermatologist. The possibility of sexual abuse must be considered especially if the vulvovaginitis is persistent or recurrent after adequate treatment.

The vaginal mucosa is affected by maternal oestrogens at birth; this gradually decreases until about 6 months of age. Thereafter until menarche the mucosa is thin and atrophic and vulnerable to infection.[1] In addition the vaginal orifice is less well protected by the labia in childhood, and its proximity to the anus combined with poor hygiene in small children adds to the risk of vulvovaginitis. Constipation and the leakage of faeces or flatus also leads to irritation and infection.

There is now increasing concern over sexual abuse of children. Among signs associated with sexual abuse by some are genital itching, soreness and vaginal dischage,[2 3] although others have questioned the sensitivity and specificity of such a finding.[4 5] There is some information available on vaginal discharge and vulvovaginitis in children in the USA[1 6 7] but little or none from the UK.

We have undertaken a prospective survey of girls attending the accident and emergency departments of the Royal Liverpool Children's Hospital (Alder Hey and Myrtle Street branches) with the complaint of vaginal discharge and/or genital irritation or soreness, in order to obtain information on its epidemiology, microbiology, and clinical features.

Patients and methods

The Royal Liverpool Children's Hospital accepts children from birth to 16 years, and the accident and emergency departments have an attendance rate of 68 000 new patients each year. From July 1987 to March 1990 all of the 200 girls presenting with a complaint of genital itching or soreness, vaginal pain, vaginal discharge or dysuria (without clinical evidence of urinary tract infection) were entered into the study. At the initial visit or at the first follow up they were each seen by a senior doctor in the department: usually (96%) a consultant experienced in both paediatric accident and emergency work and also in child sexual abuse. For each child a full medical and social history was obtained, and the possibility of child sexual abuse was considered.

A full medical examination was done, a midstream specimen of urine, and one or two swabs of either the vaginal introitus or the vestibule were obtained from each child where possible. (Even gentle swabbing of the vaginal area may cause discomfort and if the child objected we did not insist on a second swab.) In addition a Sellotape slide test to detect the presence of threadworms was done on each child (after the procedure had been explained to the mother) on the morning she was due to return for follow up.

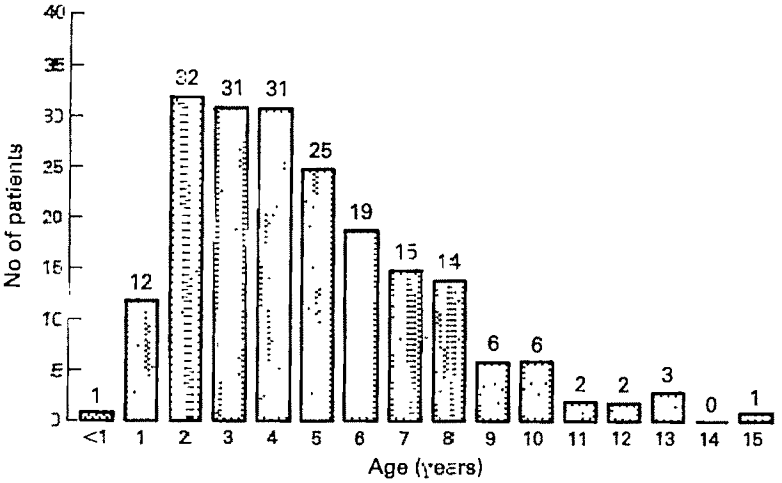
Urine was examined for pus cells, protein, and bacteriuria according to standard methods, including urine culture.

A Gram film was made from the swabs and then the swabs were cultured on blood agar, chocolate agar, gonococci selective media, MacConkey agar, Sabouraud's agar, aerobically (with 10% carbon dioxide), and neomycin blood agar anaerobically. Thus the pathogens sought were staphylococci, streptococci, coliforms, gonococci, gardnerella, *Haemophilus influenzae*, and candida. For the first half of the survey the second swab was placed in *Trichomonas vaginalis* medium and in the second half this was replaced by a swab for the detection of *Chlamydia trachomatis*. This was done by both culture (McCoy cells) and antigen detection (Syva UK).

Treatment was given according to clinical and laboratory findings. Skin problems were referred to the dermatology clinic for diagnostic confirmation and treatment. Ultrasound examination of the urinary tract was performed if there was significant bacteriuria, and if symptoms persisted patients were referred to the renal clinic. Examination under anaesthesia was undertaken if the vaginal discharge was persistent, foul, or bloody.

Results

The age range of the girls was from 1 to 15 years



Number of patients for each year of age at presentation.

(figure) but 138 (69%) were aged 2 to 6 years. Although 71 had an acute onset, 54 had a history covering more than six months, and 42 had recurring problems.

All the girls were asked to return for follow up and only two did not do so. They each had a brief history, were diagnosed as having thrush, and given treatment. The diagnosis was later confirmed in one case when the swab result became known.

Table 1 Clinical features of children presenting with vulvovaginitis

Features	*No (%)*
Symptoms:	
Itch	81 (40)
Soreness	108 (54)
Bleeding	37 (19)
Discharge	104 (52)
Signs:	
Genital redness	167 (84)
Visible discharge	66 (33)
Perianal soiling	35 (18)
Specific skin lesion	28 (14)
None	5 (2·4)

The presenting symptoms and findings on examination are shown in table 1. Secondary symptoms of abdominal pain in 51 (26%) and dysuria with or without frequency in 102 (51%) were seen. The findings of perianal soiling and visible discharge were more frequent in children presenting later in the day, for example after school, when their underwear had not been changed. Of the five girls in whom nothing abnormal was found on examination of the genitalia, three had threadworms, one was constipated, and one had poor hygiene.

Specific skin lesions include 14 girls with labial adhesions, five of which were complete. They caused particular problems with dysuria and soreness. Lichen sclerosus et atrophicus accounted for five cases, warts for three, flexural psoriasis for two, flexural eczema three, and ammoniacal dermatitis one. The vulva of one child was replaced by a large haemangioma, causing pooling of urine in the vestibule and subsequent infection.

Table 2 Number of patients investigated (n=190)

Investigation	*No (% of total)*	*Abnormal result (% of tests)*
Bacterial swab	160 (84)	88 (55)
Trichomonas swab	99 (52)	0
Chlamydia swab	23 (12)	0
Sellotape slide test or worms seen	133 (70)	43 (32·3)
Midstream urine		
Microscopy	167 (88)	40 (24)
Culture	167 (88)	20 (12)
Ultrasound of abdomen	32 (17)	3 (9·4)
Examination under anaesthesia	13 (6·8)	3 (23)
No investigation	10 (5)	

Table 2 shows the numbers of patients undergoing each investigation, and the number with abnormal results. No investigations were done on 10 girls because it was thought to be unnecessary. Treatment was given without prior investigation to three girls with complete labial adhesions. A further five were referred directly to the dermatologist, three with perianal warts, and one each with psoriasis and lichen sclerosis. The remaining two patients had clinical candida and scarlatina respectively, and treatment was started immediately.

The three abnormalities found on ultrasound were a ureterocele, ureteric reflux, and a mild dilatation of the right collecting system, and these children were referred to the appropriate clinic.

Examination under anaesthesia was undertaken if the discharge was recurrent and did not respond to treatment, or if there was significant bloodstaining. A small piece of paper was found in the vagina of each of two sisters. The younger child later had a recurrence of purulent discharge, further foreign bodies were found, and she was referred for psychological assessment. No other child had a foreign body but high vaginal swabs grew *H influenzae* in three cases, β-haemolytic streptococcus in one, and *Escherichia coli* or faecal flora in two.

Table 3 Abnormal results of vaginal swab and coincident findings of threadworms and urine culture

Organisms cultured	*No of positive cultures*	*Threadworms*	*Midstream urine*	
			Positive culture	*Sterile pyuria*
E coli/faecal flora	23	6	3	3
H influenzae	20	5	3	7
H influenzae+*Proteus* sp	2	1	0	0
S aureus	14	5	0	3
Streptococci	17	2	2	3
Candida	7	0	0	2
Pseudomonas	1	1	0	0
Klebsiella sp	3	0	0	0
Proteus sp	1	0	1	0
Total	88	20	9	18

MICROBIOLOGICAL RESULTS

No child had a positive result from the trichomonas or the chlamydia swabs. Of the 43 children with threadworms, 34 had ova on the Sellotape slide test, and threadworms were seen in nine children, either in the stools or on examination of the anus.

Table 3 shows the relationship between the organism found on bacterial swab culture, and the presence of threadworms, a positive urine culture, or sterile pyuria. Candida was found in seven children. Six were at extreme ends of the age range, two being less than 2 years and four pubertal, and the seventh child was 9 years old and had flexural psoriasis of the genital region.

Girls who had been given several courses of antibiotics before presentation and who continued to have problems responded to nystatin treatment, although *Candida albicans* was not found on culture. A herpetic rash of the vulva was seen in three patients, but virology swabs were negative in two of them. However, one of these children also had a 'cold sore' on her finger that responded to acyclovir, and the other grew β-haemolytic streptococcus in her bacterial swab. The third child was proved to have herpes simplex virus type 1. In the swab cultures *Staphylococcus aureus* was also grown with *Klebsiella* sp in one child and with β-haemolytic streptococci in five others. Of the 17 positive streptococcal cultures, 14 were β-haemolytic streptococcus group A, one was group B, and two were *Streptococcus pneumoniae*.

Sellotape slide test

The total number of children with proved threadworm infestation was 43, including nine who had no Sellotape slide test, but in whom adult worms were seen on examination or in the stools. In one child ova were seen on the slide and in the urine. All other tests were negative in 23 of those with threadworms. Organisms were grown in the vaginal swabs of 20 (46·5%) of the children with threadworms (table 3). In addition, six had sterile pyuria and six an *E coli* bacteriuria.

Urine microscopy and culture

A sterile pyuria was defined as a white cell count of at least 50×10^6/l with no significant bacterial growth on culture. It was found in 40 patients, 17 of whom had cell counts greater than 200. Threadworms were present in six girls and 18 had a positive growth on vaginal swab culture (table 4). Among the girls with pyuria were two girls with an acute throat infection, five with constipation requiring treatment, and two with labial adhesions (not shown in table). The child with the ureterocele also had sterile pyuria.

Table 4 shows the symptoms and findings associated with these cases and with 20 whose urine had a significant bacteriuria. It will be noted that discharge and abdominal pain were more frequent complaints in the group with pyuria, while dysuria and frequency were more common in those with a bacteriuria. A high cell count was more common in the infected urines.

Table 4 Urine microscopy and culture in relation to symptoms and findings

	Sterile pyuria (n=40)	*Positive culture (n=20)*
Symptoms:		
Discharge	29	8
Dysuria	21	15
Frequency	4	5
Fever	4	3
Abdominal pain	18	6
Findings:		
White cell count >200×10^6/l	17	12
Threadworms	6	6
Positive swabs	18	9
Labial adhesions	2	3
Skin problems	3	1

The organisms grown in the vaginal swabs of both groups are seen in table 3.

Significant bacteriuria was present in 20 cases (table 4), 15 of which grew *E coli* two *Proteus sp*, and one each *Staphylococcus epidermidis, H influenzae,* and β-haemolytic streptococcus. Of these children with positive urine cultures nine also had positive swab cultures, there were threadworms in six, three had labial adhesions and one child had lichen sclerosis. Of the cases of *Proteus* sp bacteriuria, one was associated with complete labial adhesions, and the other who had a haemangioma also had *Proteus* sp in the vaginal swab. The patients who grew *H influenzae* and β-haemolytic streptococcus in their urine each had the same organism cultured from their vaginal swabs. Ultrasound examinations on 11 of these girls were normal, and four who were referred to the urology clinic showed no renal abnormality.

SEXUAL ABUSE

The possibility of abuse was raised with all the parents and with the girls who were old enough. Many parents were already concerned about the subject and seemed relieved to discuss it. In most of the children there was no reason to suspect abuse. In two there had been previous abuse but no evidence of recurrence, and candida was grown in one girl who had had voluntary intercourse. There was no evidence of abuse in four others who were brought because their symptoms made adults suspicious. The diagnosis in these children was urinary infection in one, flexural psoriasis in one, and very poor hygiene in two cases. In four cases the doctor's suspicions were aroused. A 3 year old had an introitus which dilated to 1 cm in diameter but the hymen was intact. She had threadworms and the dilatation disappeared after treatment so it was, after consultation, felt to be probably within normal limits. Odd behaviour in one child, late reporting of an associated injury in another, and the child with the multiple foreign bodies in her vagina all gave cause for concern. In none of these was abuse substantiated after investigation. A vague history of touching was obtained in two small girls but examination was negative. Two children with recurrent discharge later disclosed abuse but their original presentation was not appreciably different from the rest of the children in the series.

Discussion

Vulvovaginitis has many causes in young girls especially in the 2 to 6 year age range when hygiene is poor. Soreness and itch leads to rubbing or scratching so adding infection to already compromised skin. Rubbing or fingering the area by an adult might be expected to cause similar problems but increased vascularity and erythema were found less in sexually abused children than in a symptomatic non-abused group by Emans *et al.*[4] The poor hygiene found in many of our patients confirms the opinion of other authors who considered it to be an important cause of vulvovaginitis in children.[1 7]

The microbiology of the paediatric vagina was studied in 100 healthy girls by Hammerschlag *et al.*[6] They found diphtheroids and *S epidermidis* to be the most common organisms, and candida was found only in the infants or the pubertal children. Paradise *et al*, in comparing children with vulvovaginitis and controls found candida only in pubertal girls but said convincing evidence of bacterial or candida infection was found in half of the patients with discharge and in none of those without.[7] Very few isolates of *H influenzae* or β-haemolytic streptococci were found. In our series the cultures of candida were confined to infants and teenagers except for one child who had lichen sclerosis. We found no trichomonas, chlamydia, or gonococci in our investigations although they have been found by others in a few cases.[6 7]

H influenzae and β-haemolytic streptococci are thought to be pathogenic organisms in the vaginal region in children. Macfarlane and Sharma found *H influenzae* in children with vulvovaginitis but not in controls.[8] This was the most common single organism in our series and was also found in the high vaginal swabs of three of the 13 girls who were examined under anaesthesia. Group A β-haemolytic streptococci were isolated in 14 of our cases. The literature reviewed by Straumanis and Bocchini, describing 27 patients, showed that the vulvovaginitis caused by this organism was acute in onset and often associated with an upper respiratory infection,[9] this agrees with our experience.

Threadworms are said to be a common cause of vulvovaginitis,[1] and we found them in 32·3% of cases tested. Almost half of them were associated with a positive vaginal swab culture and some with a significant bacteriuria or sterile pyuria; thus, they are an important cause of morbidity in children.

Dysuria and frequency are often assumed to be due to a urinary tract infection and antibiotics given for it, sometimes repeatedly. In a review of 53 adolescent girls with dysuria only 17% were found to have a urinary tract infection, while 41% had vaginitis, and 25% other local causes.[10] Dysuria and frequency were frequent complaints in our patients. In patients with significant bacteriuria, contributory factors such as threadworms, discharge, or local problems were present in 18 of 20 cases.

On physical findings alone, sexual abuse is difficult to distinguish from vulvovaginitis due to other causes, in the absence of other factors such as sexually transmitted organisms found on vaginal swab culture, concerns about behaviour or social conditions, or a disclosure by the child. However, if the discharge or vulvitis is persistent or recurrent in spite of adequate treatment the possibility must be seriously considered. Genital warts are said to be diagnostic of sexual abuse and these cases require careful consideration, but the virus may be spread from warts on the hands of child or carers, especially if the genital skin is already compromised. As typing of the virus becomes more common the diagnosis of sexually transmitted wart infection will become easier.

Some practical lessons have been learned from this survey of children with vulvovaginitis. A full history and examination including an inspection of the genital area should be done on all girls complaining of soreness, itch, dysuria or discharge. With the help of a gynaecologist, we have produced a printed sheet with instructions on hygiene to be given to parents. If there is no clinical evidence of an acute urinary tract infection, treatment may be delayed until the laboratory results of urine and swab cultures and Sellotape slide test are obtained. Meanwhile simple hygienic precautions may considerably relieve the child's distress.

Antibiotics should be given if there is a growth of *H influenzae* or β-haemolytic streptococci. Threadworms or significant constipation should receive the standard treatment. Local skin problems are not uncommon in vulvovaginitis and help from the dermatologist should be sought promptly. A foreign body in the vagina is an uncommon finding but examination under anaesthesia is necessary if discharge is foul or bloodstained and persists or recurs after adequate treatment.

We wish to thank Miss WJ Robson and Dr EM Molyneux, consultants in the accident and emergency department for their help and encouragement, and Miss A Garden, paediatric gynaecologist for the preparation of the leaflet on hygiene

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Archives of Disease in Childhood 1992; 67: 513–516

Growth in patients with isolated gonadotrophin deficiency

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Accepted 27 November 1991

Abstract

The growth pattern of 66 patients (50 males, 16 females) with isolated gonadotrophin deficiency (IGnD), who had reached their final height with epiphyseal closure, was evaluated. For the purpose of analysis the males were divided into two groups according to age at referral: group 1 <16 years ($n=23$) and group 2 $\geqslant 16$ years ($n=27$). Sex hormone treatment was initiated at a mean (SD) chronological age of 15·8 (1·3) and 18·6 (1·2) years in groups 1 and 2 in the males and at 15·3 (1·3) years in the females. The duration of treatment (until epiphyseal closure) in the males was 3·9 (1·5) years in group 1 and 2·1 (1·0) years in group 2 and 2·8 (1·3) years in the females. There was no significant difference between the mean final height in groups 1 and 2, but it was significantly higher than the mean parental height (mean height SD score (HtSDS): 0·1 (1·1) *v* −0·8 (0·9)) and they were significantly correlated. For females the mean HtSDS compared with parental height was 0·4 (1·5) *v* −0·6 (1·2).

It is concluded that the timing of induction of puberty by sex hormones in males and females with IGnD has no significant effect on final height provided that moderate doses are used. Furthermore final height was significantly correlated to mid-parental height.

Patients with isolated gonadotrophin deficiency (IGnD) often present a diagnostic problem because of the difficulty in differentiating between it and idiopathic delayed puberty in the prepubertal period.[1 2] Referral for endocrine evaluation and treatment is thus often delayed. Although growth of IGnD patients is usually described as normal,[3 4] at the age of puberty there is a slowing of the growth rate. The effect of timing of the initiation of sex hormone replacement therapy is controversial.[5]

We carried out a retrospective analysis of the growth pattern of a large group of patients of both sexes with IGnD who have reached final height.

Subjects and methods

We studied 66 patients (50 males, 16 females) with IGnD of idiopathic origin who were followed up from prepuberty to completion of puberty and achievement of final height. They were referred to our clinic for evaluation of delayed puberty, hypogenitalism, or slowing of growth. Anosmia was diagnosed in 13 males and three females; five of them (four males, one female) belonged to two families. Three males aged 2 months to 4 years were siblings of known patients with Kallmann's syndrome and during follow up for hypogonadism and hypogenitalism were eventually diagnosed as having Kallmann's syndrome. Patients with multiple pituitary hormone deficiencies, central nervous system tumours, or other hypothalamic pituitary disorders, adrenal or thyroid disease, or primary gonadal failure, were excluded. Patients with IGnD who had received previous hormonal treatment at other clinics were also excluded. The diagnosis of IGnD was confirmed in all patients at final height and epiphyseal closure by discontinuation of sex hormone treatment for 6–12 months and documenting the following: no spontaneous testicular growth and low plasma testosterone concentrations in the males, no spontaneous menstruation and a low plasma β oestradiol in the females, and absence or prepubertal response of luteinising hormone and follicle stimulating hormone to gonadotrophin releasing hormone stimulation in both sexes.

Height was measured by a trained nurse with a wall mounted Harpenden stadiometer. Pubertal rating of pubic hair and genitals for the males and of the breast for the females was performed according to Tanner's criteria.[6] Bone age was estimated from radiographs of the left hand and wrist using the atlas of Greulich and Pyle for carpal and phalangeal bones.[7]

Upon referral all patients underwent a comprehensive work up, including routine physical examination and determination of plasma concentrations of sex steroids, gonadotrophins, and prolactin (all assessed by routine radioimmunoassay methods). The diagnosis of IGnD was established by lack of response of plasma luteinising hormone and follicle stimulating hormone to single and repeated gonadotrophin releasing hormone stimulation.[8] In the males the response of testosterone to human chorionic gonadotrophin (1500 U given intramuscularly on three alternate days) and in the females the response of oestradiol to human menopausal gonadotrophin (75 U given intramuscularly on three alternative days) were also tested. Data were obtained on parental height. Sex corrected mid-parental height was calculated by adding or subtracting 6·5 cm from the mean parental height (cm) for males and females, respectively. Patients were seen for follow up at intervals of three to six months. Bone age was estimated upon referral and thereafter at intervals of six to 12 months until complete closure of epiphyses of the hand and wrist. Age at termination of puberty and achievement of final height was considered to be that at which growth velocity was less than 1 cm/year and the epiphyses of the hand and wrist were fully ossified.

Puberty was induced as follows: the males received a testosterone depot preparation (Testovirone, Schering), 100 mg intramuscularly monthly and after stage 3 puberty at a dose of 250 mg/month. The females were given conjugated oestrogens (Premarin, Ayerst), 0·625 mg/day and after stage 4 puberty at a dose of 1·25 mg/day, with the addition of medroxyprogesterone acetate (Oragest, Teva), 10 mg/day for seven days each month, on day 21 of the cycle once vaginal bleeding had occurred. Treatment was maintained throughout the follow up period.

Duration of induced puberty in years and total pubertal growth in cm were calculated by subtracting the age and height respectively at initiation of sex hormone treatment from that at achievement of final height. Also calculated were the growth velocity during the year before initiation of treatment (GV_0) and that during the first year of treatment (GV_1). Standing height was expressed in actual measurements (cm) and in standard deviation score (HtSDS), using Tanner's SD tables.[9] Parental HtSDS was calculated from the sex corrected mid-parental height by the same method, using the highest age available in the SD tables. Bone maturation index was calculated from the pretreatment and treatment periods using the equation Δ bone age: Δ chronological age.

Statistical analysis of the results was performed using the paired or unpaired Student's *t* test with two tailed significance levels for comparison of differences between means of longitudinal or mixed groups respectively, and simple linear regression and correlation tests for evaluation of the relationships between various parameters. Outliers were not eliminated from the data sets. All data are presented as mean (SD) unless otherwise specified.

Table 1 Distribution of age at referral of males and females with IGnD

Age (years)	*No (%) of males (n=50)*	*No (%) of females (n=16)*
0–1 0	1 (2)	—
1 1–4 0	2 (4)	—
4·1–6 0	—	—
6 1–8·0	6 (12)	—
8 1–11·0	3 (6)	—
11 1–13·0	5 (10)	7 (44)
13 1–16 0	6 (12)	5 (31)
16·1–18·0	8 (12)	4 (25)
13 1–20 0	17 (34)	—
>20 0	2 (4)	—

Results

As can be seen from table 1 there was a considerable difference between the males and females. Whereas the range for the males was very wide, from birth to 22 years (23 were referred below age 16 and 27 at age 16 years or older), the range in the females was from age 12 to 18 years. As the age at which sex hormone treatment was initiated was significantly influenced by the age at referral the pertinent clinical and laboratory data at referral (table 2) and during follow up (table 3) are given separately for the two age groups for the males.

The mean basal plasma concentrations of sex hormones and prolactin were within the normal prepubertal range for both sexes (table 2). In the males the mean peak plasma testosterone response to human chorionic gonadotrophin was significantly lower than in normal prepubertal boys aged 10–14 years (8·1 (2·6) nmol/l; $p<0·002$). Treatment with sex hormones was initiated at a bone age of 11–15 years in the males and 10–14·5 years in the females, subject to the age at referral (table 3). At the onset of induction of puberty the males referred below the age of 16 years (group 1) had attained a mean (SD) of 91 (2)% of their final height whereas those referred at 16 or older and the female patients had attained 95 (2)% of their final height.

The mean growth velocity was similar in all patients in the year before initiation of treatment (GV_0) and increased significantly in the two male groups ($p<0·02$) during the first treatment year (GV_1). The mean GV_1 and mean changes in growth velocity over the first treatment year (GV_1-GV_0) were highest in the younger males (group 1) and lowest in the females (table 3). The mean maximal growth velocity (GV_{max}) achieved at a bone age corresponding to that of boys with normal puberty[10]

Table 2 Pertinent clinical and laboratory data of 66 isolated hypogonadotrophic patients at referral

Variable	*Males*		*Females (n=16)*
	Group 1 (n=23)	*Group 2 (n=27)*	
Mean (SD) chronological age	8·9 (5 2)	17·5 (1·0)	14 6 (1·5)
Median (range)	7 5 (0·2–15·5)	17 9 (16·1–22 2)	14·2 (12–18)
Mean (SD) bone age (years)	7 7 (4·3)	14 0 (1·0)	11 5 (1·5)
Median (range)	6·7 (0–12)	13·5 (10–15 5)	11·0 (9–14)
Mean (SD) height (cm)	122 0 (31·0)	164·0 (8·8)	150 4 (7·3)
Mean (SD) HtSDS	−0·8 (1 3)	−1·1 (1·2)	−1·3 (1·6)
Pubic hair (Tanner 1–5)	1–3	1–4	1–3
Testicular volume (ml)	0 5–2·5	1–3	—
Breast stage (Tanner 1–5)	—	—	1–2
Mean (SD) testosterone (nmol/l)*			
Basal	0 3 (0·1)	0 5 (0·2)	
Peak	3·3 (1·1)	4 7 (0 9)	
Mean (SD) 17 β oestradiol (pmol/l)†			
Basal	—	—	51 4 (14·7)
Peak			220·3 (132·2)

Group 1: age at referral <16 years and group 2: age at referral ≥16 years.

*Plasma testosterone (peak concentration after human chorionic gonadotrophin 1500 U on three alternate days.

†Plasma 17 β oestradiol (peak concentration after human menopausal gonadotrophin 75U on three alternate days.

Table 3 Effect of treatment on growth in isolated hypogonadotrophic patients

Variable	*Males*		*Females (n=16)*
	Group 1 (n=23)	*Group 2 (n=27)*	
Chronological age at initiation of treatment	15·8 (1·3)	18·6 (1·2)	15·3 (1·3)
Bone age at initiation of treatment	12·6 (1·2)	14·6 (1·0)	12·6 (0·8)
Height (cm)	157 (13·8)	169 (8·5)	156 (9·2)
HtSDS	−1·4 (1·1)	−0·8 (1·3)	−1·1 (1·5)
GV_0 1 year (cm/year)	4·0 (1·3)	4·5 (2·0)	4·0 (0·7)
GV_1 (cm/year)	5·7 (1·1)	5·3 (1·7)	4·4 (1·5)
$GV_1 - GV_0$ (cm/year)	1·8 (0·2)	1·1 (0·3)	0·9 (0·4)
Treatment period (years)*	3·9 (1·5)	2·1 (1·0)	2·8 (1·3)
GV_{max} (cm/year)	7·2 (1·3)	6·0 (1·5)	4·7 (1·0)
Chronological age at GV_{max} (years)	17·0 (0·9)	19·2 (0·5)	16·9 (1·0)
Bone age at GV_{max} (years)	14·0 (0·5)	15·2 (0·7)	13·0 (1·1)
Total pubertal growth (cm)†	15·8 (4·0)	7·5 (2·3)	10·0 (4·8)
Bone age maturation index pretreatment‡	0·7 (0·4)	0·9 (0·5)	0·7 (0·4)
Bone age maturation index during treatment	1·3 (0·4)	1·6 (0·5)	1·3 (0·5)
Final height (cm)	172·7 (6·9)	176·6 (7·8)	164·7 (9·3)
Final HtSDS	−0·3 (1·0)	0·3 (1·2)	0·4 (1·5)
Chronological age at final height (years)	19·7 (1·0)	20·7 (0·6)	18·2 (0·5)
Mid-parental height (cm)§	168·1 (5·8)	171·0 (5·6)	158·0 (7·0)
Mid-parental HtSDS	−1·0 (0·9)	−0·6 (0·8)	−0·6 (1·2)
Final height − mid-parental height (cm)	4·9 (0·9)	6·3 (1·8)	6·2 (3·0)

*Until epiphyseal closure
†Total pubertal growth from initial treatment to epiphyseal closure
‡Bone age maturation index Δ bone age Δ chronological age
§See subjects and methods.

was also higher in the males referred at a younger age than those referred beyond age 16 ($p<0\cdot05$) and than in the females ($p<0\cdot05$).

The duration of induced puberty was longest in the younger male group ($p<0\cdot001$), similar to the normal pattern of puberty in males, and shortest in the females (table 3). The mean total pubertal growth was significantly greater in the younger males than in the older males and in the females ($p<0\cdot0001$) and lowest in group 2 of the males. The bone maturation index increased significantly ($p<0\cdot01$) in all patients during the treatment period as compared with their pretreatment values (table 3). The mean final HtSDS was close to the mean normal range in all groups (table 3) and significantly higher than at initiation of treatment ($p<0\cdot001$). The mean final height was also higher than the mean mid-parental HtSDS in all groups ($p<0\cdot05$). There was no significant difference in the mean final HtSDS between the younger and older male groups.

The correlation regression analysis revealed that the most significant factor affecting the induced pubertal growth in both sexes was the bone age at initiation of sex hormone treatment (table 4). It did not, however, affect the final height. The height of patients, both at initiation of sex hormone treatment and upon achievement of final height, was found to be significantly correlated with the mid-parental height (all patients $r=0\cdot62$, $p=0\cdot03$ and males: $r=0\cdot64$, $p=0\cdot02$; females: $r=0\cdot67$, $p=0\cdot01$, respectively).

Discussion

Patients with IGnD provide a clinical model for the evaluation of the role of gonadotrophins in prepubertal growth and of sex hormones in achieving maximal final height. It has been well documented that a close relationship exists between puberty and growth, and that sexual development, whether spontaneous or induced, is associated with a rise in plasma growth hormone and insulin-like growth factor-1 (IGF-I).[11–14] The rise in IGF-I concentrations during puberty is mediated by the gradual increase in growth hormone secretion induced by the rising concentration of sex hormones. The relatively short stature of our IGnD patients upon referral before initiation of sex hormone treatment may reflect a low pituitary growth hormone output and a low plasma IGF-I concentration due to insufficient secretion of sex hormones during the pretreatment period.[15–17]

Our review of this large series of both sexes showed that IGnD tends to be diagnosed at an earlier age in boys than in girls. This is due to the fact that hypogonadism and hypogenitalism are more readily apparent in the male. This difference led to earlier initiation of sex hormone treatment in some of the boys (group 1).

Table 4 Correlation matrix of growth related variables in males and females with IGnD

	HtSDS at start of sex hormone treatment	*Duration of induced puberty*	*Total pubertal growth*	GV_{max}	*HtSDS at termination of induced puberty*
Bone age at start of sex hormone treatment					
Males					
r	0·78	−0·50	−0·80	−0·52	0·21
p	0·001	0·02	0·0001	0·008	0·10
Females					
r	0·65	−0·65	−0·90	−0·28	0·24
p	0·01	0·01	0·0001	0·09	0·20

This study confirms previous reports that IGnD patients of both sexes achieve a normal final height.[3,4] In the males institution of treatment with a low dose (100 mg/month) of a depot preparation of testosterone and progressively increasing the dose up to 250 mg/month resulted in a comparable final height whether treatment was initiated at an earlier or later age. However, the earlier initiation of treatment in the boys in group 1 resulted in a longer period until ossification of the epiphyses had been completed and in a greater height gain during the period of induced puberty, as compared with the boys in group 2. The latter were, however, taller upon initiation of treatment, which compensated for the lesser growth during the period of induced puberty and the result was a similar final height in both these groups. These results are in agreement with those of Bourguignon who compared the effect of sex hormone induced puberty on final height in hypopituitary patients with growth hormone and gonadotropin deficiency with that in hypopituitary patients with spontaneous occurrence of puberty.[5,18]

The females with IGnD showed a growth pattern similar to that of the group 2 males. In both the females and the group 2 males chronological age and bone age at referral and initiation of treatment were relatively greater than in the males of group 1.

The importance of the genetic influence on growth is reflected in the significant positive correlation between the height of the patients, both pretreatment and final height, and the sex corrected mid-parental height. Most of the patients with IGnD, and particularly the females, achieved a significantly taller final height than the sex corrected mid-parental height. This can be explained partly by the effect of the secular trend of the general population. Pescovitz in a review of the endocrinology of the pubertal growth spurt, suggests that in IGnD the absence of gonadal sex steroids results in a delayed pubertal growth spurt and probably a small but significant increase in final adult height.[19] The fact that at initiation of sex hormone treatment the height of patients was relatively short in comparison with the mid-parental height and that there was a height gain of 1 SD during the period of treatment supports the suggestion that with low to moderate doses of sex hormones, such as used in the present study, there is initially more effect on linear growth than on bone maturation.[20,21]

Of interest among the findings in this study is the fact that plasma testosterone response to human chorionic gonadotrophin stimulation in the males with IGnD was significantly lower than in normal boys at comparable pubertal stages, indicating the usefulness of this test to distinguish between 'simple' delayed puberty and permanent IGnD states in males.

In conclusion, the results of this study indicate that IGnD patients achieve normal final height irrespective of the timing of initiation of sex hormone treatment. It is therefore suggested that the timing of sex hormone replacement treatment should be decided on the basis of psychosocial determinants.

AC was on leave of absence and recipient of a fellowship from the Pediatric Clinic, Genova University, Italy ZL holds the Irene and Nicholas Marsh Chair in Endocrinology and Diabetes at Tel Aviv University

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Archives of Disease in Childhood 1992; **67**: 517–520

Fetal haemoglobin and early manifestations of homozygous sickle cell disease

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Abstract

The relevance of fetal haemoglobin (HbF) concentration to the development of early clinical manifestations of homozygous sickle (SS) disease has been investigated by examining the time to first occurrence and the proportional hazard of these complications in three groups of the HbF distribution at age 5 years. HbF was significantly related to dactylitis, painful crises, acute chest syndrome, and acute splenic sequestration. The relationship suggested that a critically low HbF concentration increased the risk, little difference in risk occurring between the medium and high HbF groups. The abdominal painful crisis and hypersplenism were not related to HbF concentration suggesting that the degree of sickling may not be important in their genesis. Parental education on acute splenic sequestration should be focused on children with HbF concentrations in the lowest part of the HbF distribution for age.

One factor contributing to the highly variable natural history of homozygous sickle cell (SS) disease appears to be the concentration of fetal haemoglobin (HbF). High concentrations are generally associated with mild clinical courses in patients of African origin[1] and also characterise the relatively benign disease observed in the eastern province of Saudi Arabia[2] and central India.[3] However, some patients with high HbF values have severe manifestations and others with low values may be mildly affected, casting doubt on the clinical relevance of HbF concentrations.[4] A Jamaican study of SS disease in the first two years of a neonatally defined cohort has reported that low concentrations of HbF were significantly related to the early appearance of splenomegaly, and a greater incidence of dactylitis and acute splenic sequestration.[5] Observations in this study have now been extended to a median age of 12 years and to other clinical complications.

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Accepted 1 October 1991

Patients and methods

Patients participated in a cohort study of sickle cell disease based on a cord blood screening programme at the main government maternity hospital (Victoria Jubilee Hospital) in Kingston, Jamaica. Between mid-1973 and late 1981, a total of 100 000 infants were screened with the detection of 314 cases of SS disease. Of these, 308 were located and recruited to cohort clinics operated by the staff of Medical Research Council Laboratories at the University Hospital of the West Indies. Routine appointments were given at intervals of one month up to six months, two months to one year, and three months thereafter and children were encouraged to attend at any time if sick. The study group was confined to 223 subjects (119 male, 104 female) who had survived beyond 4·5 years and in whom adequate HbF estimations and clinical data were available. Of the 85 subjects excluded, 41 had died or emigrated before 4·5 years, and 44 had insufficient HbF values or clinical data. The latter group included patients with more than one year of default in whom it was assumed that recall would be inaccurate. Patients were aged 4·7–17·4 years at the time of the study and median follow up was 12 years.

The diagnosis of SS disease was based on criteria previously described.[6] Blood samples were taken by venepuncture at yearly intervals on the child's birthdate or when clinically indicated. Standard haematological methods were used. HbF was determined by an alkali denaturation method after making standard haemolysates.[7]

The relationship between HbF concentration and clinical events was investigated by dividing patients into three groups on the basis of HbF value at age 5 years. HbF values were available within six months of this target age in 223 subjects and the distribution was derived separately for the two sexes and arbitrarily divided into three groups of approximately equal size representing the low, medium, and high portions of this distribution at age 5 years (table 1). To ascertain that the HbF group at age 5 years was characteristic of an individual subject, the assignment to HbF group was compared in a subset of patients with HbF concentrations at both 5 and 10 years, and showed that the same HbF group assignments occurred in 65/83 (78%) males and in 61/83 (73%) females. All other subjects except one

Table 1 Concentrations of HbF (%) defining HbF groups in both sexes at 5 and 10 years of age

HbF group	*Males*		*Females*	
	No of patients	*Defining concentration*	*No of patients*	*Defining concentration*
Age 5 years				
Low	40	≤4·8	36	≤6·1
Medium	40	4·9–9·7	34	6·2–10·3
High	39	≥9·8	34	≥10·4
Total	119		104	
Age 10 years				
Low	26	≤2·4	30	≤3·8
Medium	28	2·5–6·3	27	3·9–7·4
High	29	≥6·3	26	≥7·5
Total	83		83	

deviated only to an adjacent HbF group. A similar analysis has also confirmed a close relationship between HbF group assignments at six months and two years.[5]

Clinical events were defined as follows. Dactylitis referred to an acute, painful, non-pitting swelling of the hands, feet, fingers, or toes with no evidence of infection. The painful crisis was defined as an episode of bone pain at two or more sites of sufficient severity to interfere with function, two sites being specified to avoid confusion with localised avascular necrosis of bone. The abdominal painful crisis referred to localised or generalised abdominal pain and tenderness, but without the characteristics of other medical or surgical conditions. Acute chest syndrome was associated with pleuritic pain, fever, cough, respiratory distress, and clinical or radiological signs of pulmonary infiltration. Acute splenic sequestration was defined according to the expanded definition of Topley *et al* involving acute splenic enlargement,[8] a fall in haemoglobin concentration of at least 20 g/l, and evidence of increased bone marrow activity. Hypersplenism applied to sustained splenic enlargement of 4 cm or more associated with haemoglobin concentrations below 65 g/l, and platelet counts below 260× 10^9/l on at least two occasions six months or more apart.

The incidence of these clinical events in the two sexes in the different HbF groups was initially examined by the survival curve method, which allows for changes in the population at risk from death, default, or emigration, and the relative risks compared by the log rank test. Significance of the association between clinical events and HbF group was assessed by the χ^2 test for trend. All data were used in the survival analysis, although the figures presented were truncated to 10 years, to avoid the misleading effect on the survival curves of few remaining older patients.

As certain sex differences in the relationship between HbF and clinical features emerged from survival curve analysis and as the HbF distribution differed in the two sexes, these relationships were further investigated by proportional hazards regression using generalised linear interactive modelling (GLIM) and the method described by Aitkin *et al.*[9] This method has the advantage over conventional survival analysis of simultaneous adjustment for a number of potential confounding factors. For this analysis the entire study population was divided into three equal sized groups on the basis of HbF concentration at age 5 years: group I, HbF <5·4%; group II, HbF 5·4–9·7%; group III, HbF ≥9·8%. The factors entered into the model were HbF, sex, and the HbF-sex interaction.

Results

The relationships between clinical events and HbF group as assessed by survival curve analysis are shown graphically in figs 1–4 and their significance summarised in table 2.

Acute chest syndrome had occurred in 186 patients. Age at first occurrence was significantly related to HbF in both sexes and did not differ between the sexes. The survival curve data (fig 1) suggested that the group with low HbF was particularly prone with less difference between the medium and high HbF groups.

Dactylitis occurred in 113 patients. The trend with HbF was highly significant in males (fig 2A) but although the females in the low HbF

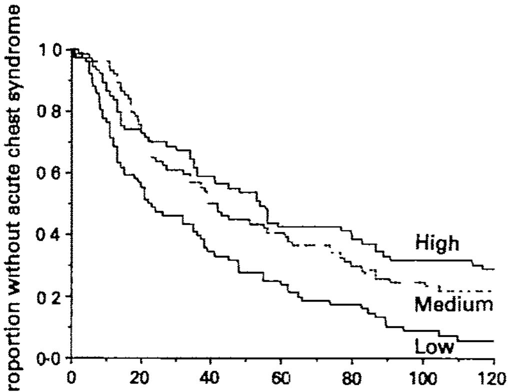

Figure 1 Survival curve analysis of the first occurrence of the acute chest syndrome in subjects of both sexes according to HbF groups.

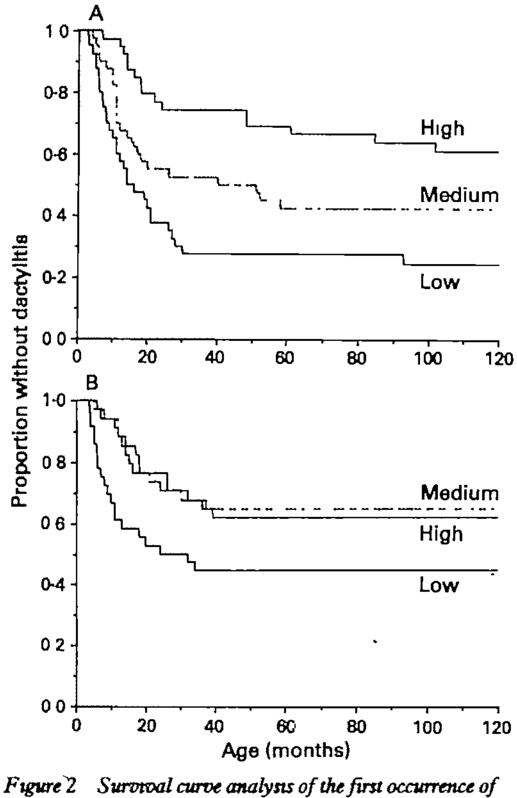

Figure 2 Survival curve analysis of the first occurrence of dactylitis according to HbF group in (A) males and (B) females.

Table 2 Relationship of clinical events with HbF group assessed by χ^2 test for trend on survival curve analysis

Event	*Males*		*Females*	
	χ^2	*p Value*	χ^2	*p Value*
Acute chest syndrome	8·07	0·005	6·30	0·012
Dactylitis	14·54	<0·001	3·45	0·063
Painful crisis	5·69	0·017	0·58	0·445
Acute splenic sequestration	14·13	<0·001	2·78	0·095
Hypersplenism	0·31	0·580	0·03	0·869
Abdominal painful crisis	0·83	0·363	1·41	0·236

group were affected earlier and more frequently (fig 2B), the trend was not significant in females.

Painful crises occurred in 157 patients. The relationship with HbF group was significant in males (fig 3A) but not in females (fig 3B).

Acute splenic sequestration occurred in 88 patients. The relationship with HbF concentration was significant in males (fig 4A) but not in females (fig 4B). As expected, most episodes occurred before 3 years of age and of those episodes occurring after 3 years, all but one were in the high HbF group.

Hypersplenism occurred in 32 patients, and there was no relationship with HbF concentration in either sex. Abdominal painful crisis occurred in 123 patients, and was not influenced by HbF group in either sex.

The apparent sex difference in the significance of HbF with some complications could have resulted from the greater proportion of males with low HbF values if a critically low concentration of HbF were an important determinant. The results of proportional hazard analysis support this as expressing the risk of complications in HbF groups II and III in relation to group I (table 3) show significantly lower risk in the higher HbF groups for dactylitis, painful crisis, acute chest syndrome, and acute splenic sequestration. Furthermore, adding sex to the model did not improve the fit indicating that these relationships were true independent of sex. Proportional hazard analysis also confirmed the lack of any relationship between HbF and abdominal painful crisis or hypersplenism.

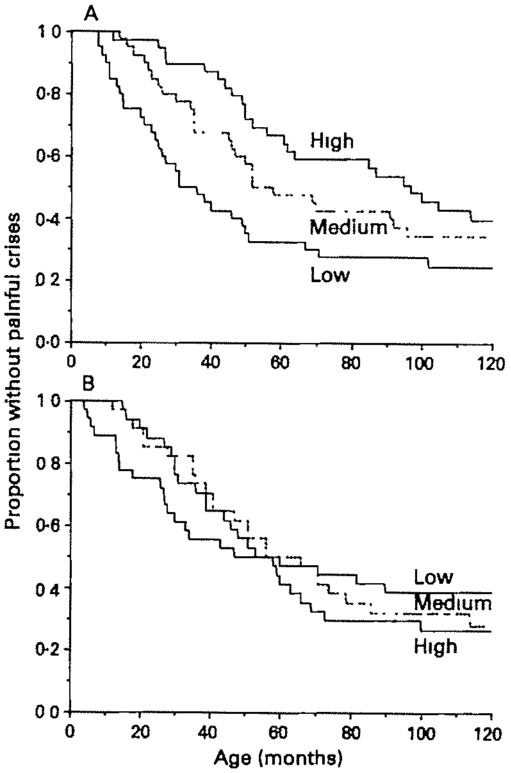

Figure 3 Survival curve analysis of the first occurrence of painful crisis according to HbF group in (A) males and (B) females.

Table 3 Hazard rates for clinical events according to HbF grouping expressed relative to group I (95% confidence intervals)

Event	*Group II (HbF 5·4–9·7%)*	*Group III (HbF≥9·8%)*
Acute chest syndrome	0·55 (0·39 to 0·78)	0·48 (0·34 to 0·69)
Dactylitis	0·39 (0·25 to 0·61)	0·32 (0·20 to 0·52)
Painful crisis	0·59 (0·40 to 0·88)	0·69 (0·47 to 1·01)
Acute splenic sequestration	0·63 (0·39 to 1·02)	0·31 (0·18 to 0·55)
Hypersplenism	0·62 (0·25 to 1·53)	0·83 (0·36 to 1·88)
Abdominal painful crisis	0·96 (0·62 to 1·49)	0·96 (0·62 to 1·50)

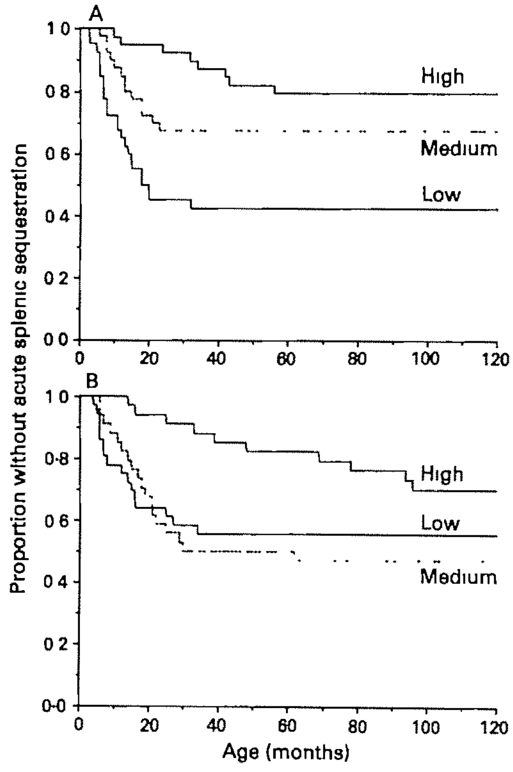

Figure 4 Survival curve analysis of the first occurrence of acute splenic sequestration according to HbF group in (A) males and (B) females.

Discussion

Previous observations in the cohort study showed that patients with low concentrations of HbF were more prone to develop dactylitis and acute splenic sequestration.[5] The present study has shown that low HbF is also a risk factor for painful crisis and acute chest syndrome. The relevance of HbF to clinical features appears to conflict with observations by Powars *et al* in Los Angeles who initially failed to find a relationship between HbF concentration and any clinical event except stroke,[4] although they later postulated that a critical concentration of HbF may protect against certain complications of the disease.[10]

Several differences in the Jamaican and American studies may have contributed to the apparently different conclusions. The present study was confined to survival curve analysis, which assesses only the timing of the first event and not the frequency of subsequent events within individuals. The Jamaican study has used clearly defined end points, which have been consistently applied from the onset of the cohort study. Furthermore the Jamaican study has used only prospectively recorded data in contrast to the American study that used inevitably less accurate retrospective data.

Finally the Jamaican population was a representative sample in contrast to the American group who were predominantly symptomatically acquired. For these reasons it seems justified to conclude that the Jamaican observations are less prone to bias.

Children in the lowest third of the HbF distribution at age 5 years were more prone to the acute chest syndrome, dactylitis, painful crises, and acute splenic sequestration. As there was a close correlation between HbF groupings at six months and two years[5] and between age 5 and 10 years, it seems reasonable to assume that the position within an HbF distribution is characteristic for an individual child. Placement within the HbF distribution may therefore be of prognostic importance for these complications and prophylactic or education programmes may be devised accordingly. For example education on parental detection of acute splenic sequestration[11] may be focused in high risk groups.

The apparent conflict between data from the survival curve analysis that showed some sex differences and that from proportional hazard analysis that did not, could be explained if a HbF value below a critical concentration was necessary as a risk factor for these complications and that this was achieved in males because of their generally lower HbF distribution.[12] This concept was supported by proportional hazard analysis that indicated that for dactylitis, painful crises, and acute chest syndrome, there did appear to be a critical concentration of HbF below which the hazard was increased.

The significant relationship between painful crisis and HbF value may appear at variance with an earlier study that failed to show a relationship between HbF and painful crisis frequency in either sex.[13] However, the end points of the two studies were different, the present study examining the age of onset of painful crises and the earlier study addressing painful crisis frequency. Both dactylitis and the painful crisis result from avascular necrosis of bone marrow and a similar behaviour to risk factors might have been anticipated. Avascular necrosis of bone marrow is likely to be influenced by both oxygen supply and demand of the expanded bone marrow. HbF concentration could influence supply by its effect on sickling and vaso-occlusion but could also influence demand if subjects with lower HbF concentrations had more rapid haemolysis and greater erythropoietic expansion.

Abdominal painful crisis and, to a lesser extent, hypersplenism appeared unrelated to HbF group The pathology of the abdominal painful crisis remains unknown but the lack of a relationship with HbF suggests that this complication is not closely related to vaso-occlusion. Low concentrations of HbF have been previously associated with the early appearance of splenomegaly[5] and high concentrations of HbF influence the persistence of palpable splenomegaly.[14] There was the suggestion of a trend between hypersplenism and HbF group in the present study but this failed to reach significance possibly because of the relatively small numbers of subjects with this complication.

The protective effect of HbF is believed to be twofold. High concentrations of HbF infer lower concentrations of sickle cell haemoglobin (HbS) within the cell but HbF molecules also participate less readily in HbS polymer formation. As a result there is an inverse relationship between HbF value and counts of irreversibly sickled cells.[14 15] The present study confirms that high and moderate concentrations of HbF determine a lower frequency and a later onset of the acute chest syndrome, dactylitis, painful crises, and acute splenic sequestration.

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Archives of Disease in Childhood 1992; 67: 521–523

Sinus histiocytosis with massive lymphadenopathy

David K Stones, Charmaine Havenga

Abstract

Sinus histiocytosis with massive lymphadenopathy is a well recognised, but rare cause of lymphadenopathy in the first decade of life. Three cases presenting with nodal disease are described. The eyelids were involved in one case. The clinical, laboratory, and biopsy findings are discussed and compared with previously reported cases.

Sinus histiocytosis with massive lymphadenopathy (SHML) is a rare cause of lymphadenopathy in children and was first described by Rosai and Dorfman in 1969.[1] The patients usually present with cervical lymphadenopathy. Multiple other lymph node groups can be involved and the extranodal manifestations of the disease are well documented. It is a disease of unknown aetiology, although some, but not all, cases have been linked to Epstein-Barr virus infection. The Epstein-Barr virus may alter the immune reaction to a specific, but unknown, antigen.[1]

The clinical features are determined by the lymphadenopathy. The signs and symptoms depend on the size, site, and number of the lymph nodes involved. The site and appearance of extranodal disease may also be characteristic.

The laboratory findings are variable and there are no pathognomonic biochemical abnormalities. The histological features are specific but the diagnosis may be easily confused with sinus hyperplasia.[1] The latter may be due to non-specific infections or infections such as cytomegalovirus, Epstein-Barr virus, rubella, mycobacterium tuberculosis, and brucella.

The prognosis is good with a mortality rate of 7%[2] and a spontaneous remission rate of 20%. There is no specific treatment for the enlarged lymph nodes.

Case report

The clinical features and laboratory investigations of the three patients are summarised in the table.

The patients were under 10 years of age and black. The history before presentation varied from three weeks to two years. The prominent feature in all three cases was appreciable cervical lymphadenopathy. In one patient the cervical nodes were smaller but there was prominent swelling of both lower eyelids and temporalis muscles. This patient also was physically and mentally retarded.

All had a raised erythrocyte sedimentation rate and platelet count. None was anaemic and two patients had a neutrophil leucocytosis. The total protein and the gammaglobulin in all three patients was increased and the raised gammaglobulin was of the IgG and IgM class.

No lymphadenopathy was evident either on radiographs of the chest or computed tomography of the mediastinum. The tuberculin skin testing was negative in all three patients.

Lymph node biopsy was performed under general anaesthesia. In all three this showed the

Clinical and laboratory results in patients with SHML

	Patient		
	1	*2*	*3*
Age (years)	1·3	5·3	8 9
Sex	M	F	M
Duration of symptoms	3 weeks	4 months	2 years
Fever (>37·5°C)	Yes	No	Yes
Clinical			
Lymph nodes	Submandibular, bilateral, 15×15 cm, hard, mobile, non-tender	Submandibular, bilateral, 7×7 cm, hard, mobile, non-tender	Submental, bilateral, 1×1 cm, hard, mobile, non-tender
White cell count ($\times 10^9$/l) [3·6–9 6]	15·9	14 0	8 3
Neutrophils ($\times 10^9$/l)	12 3	10·1	6 0
Platelets ($\times 10^9$/l) [140–440]	596	551	488
Erythrocyte sedimentation rate (mm/hour)	58	30	70
Lymphocytes (ratio TH·TS) [>1·1]	1 9	—	0 8
Globulin (g/l) [2–28]	40	33	43
Albumin (g/l) [38–52]	37	36	36
IgG (g/l) [5–13]	24	16	28
IgM (g/l) [0·5–2]	4·2	2·1	5 2

Normal results are shown in square brackets.

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Accepted 18 December 1991

classical histological features of SHML. In the patient with eyelid involvement the histological changes in the lymph node were only recognised when in addition the eyelid was biopsied. In this biopsy specimen the histiocytes showed a tendency to aggregate in solid sheets. Phagocytosis of lymphocytes with connective tissue containing prominent lymphocytes and macrophages was also seen.

One child has been lost to follow up. In the two patients who have been followed up for one year the lymph nodes have decreased in size without treatment. The child with the extra nodal involvement has also shown some resolution of his disease.

Discussion

There are to date more than 400 cases of sinus histiocytosis with massive lymphadenopathy registered in the registry at Yale University[1] Cases have been described from all continents. The three patients with the SHML described in this report show many of the clinical features as described in the literature.[1-4]

The ages ranged from 1·3 years to almost 9 years of age This is the typical age range of the disease as described previously.[2-5] Most present in the first decade of life and almost 80% by the age of 20 years.[5] The youngest case presented at birth. A male predominance has been described in the literature[1] with male to female of ratio of 2:1.[3]

The clinical features of the three patients reported are similar to the classical description of SHML. There was massive bilateral cervical lymphadenopathy in two patients, while in the third the lymph nodes were much smaller but the extranodal manifestations were more prominent. The cervical lymph nodes are involved in up to 97% of patients.[2-4] Other lymph node groups can be involved and this includes axillary, inguinal, abdominal, and mediastinal groups. The involvement is usually bilateral and painless but has been described as tender in some patients.[1] Extranodal disease occurs in 30% of patients[1 3 6] and can involve many organ systems. Sneige and Batsakis state that the nasopharynx is the most common extranodal site of the disease followed by the salivary tissue and oral cavity.[2] Foucar, Rosai, and Dorfman in a review of the literature state that skin involvement is at least as common as nasal cavity and paranasal sinus involvement.[1] One patient in this report had lower eyelid involvement, a well described entity in SHML.[1 4 5 7] This is the fourth most common site of extranodal disease.[1]

Fever is a prominent feature in some cases and two of our cases were feverish. No definite cause could be found for the mental retardation and short stature in one patient. Short stature has been described occasionally in SHML.[1]

The results of laboratory investigations have been described in detail in the literature.[1-5] The three patients reported had a raised erythrocyte sedimentation rate, two had a neutrophil leucocytosis, and the third had a normal white cell count. Anaemia is mentioned in some case reports[1 3 5] but was not present in any of our patients. Other haematological abnormalities include haemolytic anaemia and hypochromic microcytic anaemia.[1] The three patients reported had an increased platelet count, an abnormality not previously documented in the literature.

Immunological abnormalities have been described[1 2 7] and a reversal of the TH:TS (T lymphocyte helper to suppressor) cell ratio was noted. Only one of our patients had an abnormal TH:TS ratio. None of three patients had a history of abnormal infections as described by Sneige and Batsakis.[2]

Abnormalities in the serum proteins have also been described.[1] The albumin is often low and other serum proteins may also be abnormal. In the three cases reported the albumin was marginally reduced and the immunoglobulin IgG and IgM concentrations were significantly raised.

The histological features of SHML have been described in detail previously.[1-5] There are classical histological features regardless of the nodal or extranodal sites. The most prominent cells are histiocytes, which show appreciable phagocytosis. This phagocytosis is more prominent in the lymph nodes and involves lymphocytes, plasma cells, and other cellular debris. Other cell lines that are seen include lymphocytes and plasma cells. In the lymph node there is dilatation of the sinuses that is filled with the histocytes, and in the extranodal sites they arrange themselves into cords or nests to create the illusion of sinuses.[1-5] Fibrosis is often more prominent in the extranodal sites. The histology of the cases reported here showed the above features. The differential diagnosis on histological examination includes the following disease entities: metastatic melanoma, Hodgkin's disease, a variety of infectious diseases, and Langerhans' histiocytosis. In practice the most common problem is to distinguish SHML from focal nodal sinus hyperplasia that results from a wide variety of agents.[1]

In most cases treatment is not necessary as SHML is usually not life threatening or damaging to organ function. There is no specific treatment for the disease and some cases have been treated with systemic immunosuppression,[4 8 9] local excision,[4 9] and even with radiotherapy.[4 8] These treatments have been reserved for those cases with life threatening complications related to either the patency of the airways[9] or central nervous system dysfunction.[4 8] In some cases patients have requested surgery because of the massive disfiguring lymphadenopathy.[8] Many chemotherapeutic drugs have been used,[2 8] both alone and in combination. It appears that use in combination has the best results, although the remission figures do not approach those seen with malignant haematological disease. Radiotherapy also gives poor results.[8]

In conclusion this series of three patients conforms to the typical features of SHML as described in the literature. Although it is an uncommon cause of lymphadenopathy the implications are important for the patient, particularly with regard to the prognosis and management. An abnormal feature in all of the three patients reported that has not been described previously is a raised platelet count or thrombocytosis.

The authors wish to thank GJ Viviers, chief medical superintendent of Pelonomi Hospital, for permission to publish

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Proselytising neurodevelopmentalists

Here's a philosophical question for you. Can open mindedness and evangelism coexist? The question came to mind when I received through the post a copy of a magazine called *Early Age* which is to be published quarterly by a firm of marketing consultants in Halifax. The purpose of the publication is to promote the work of Dr Ferenc Katona and his team at the Budapest department of developmental neurology and rehabilitation (how many evangelical neurodevelopmental departments can a single city produce?). The author, or authors, of the articles is not stated but we are told from the start that 'on paper at least', the department is 'gaining an international reputation as a leading centre of excellence in the precise diagnosis of abnormal brain development at a very early age'. An intriguing phrase that, 'on paper at least'. Presumably it means that people write about the excellence but never talk about it. Undercover writing I suppose. Strange. A few pages later the virtues of open mindedness and eclecticism are extolled. Other schools make the mistake of stressing 'the singular importance of their own method'. Dr Katona's school, of course, would never do such a thing. Modesty would forbid it. But if you would like to attend a seminar in London, go on a six day course in Budapest, or subscribe to the newsletter, they will be prepared to share their internationally reputed (on paper) excellence with you. But only if you want to. Is my temporal lobe misbehaving or do you get that *déjà vu* feeling too?

ARCHIVIST

Archives of Disease in Childhood 1992; **67**: 524–526

T cell immunodeficiency in dyskeratosis congenita

B W Lee, H K Yap, T C Quah, A Chong, C C Seah

Abstract

Dyskeratosis congenita has been found to be associated with abnormal immune function. In this study we report a patient with this association. He developed *Pneumocystis carinii* interstitial pneumonia, and impaired cell mediated immunity was confirmed by the presence of depressed lymphoproliferative responses to in vitro stimulation with mitogen. Enumeration of T cell subsets showed a severely depressed CD4:CD8 ratio (0·38), which is the likely cause for impaired cell mediated immunity. The T cell activation pathway appeared intact, as his T lymphocytes were able to express activation markers (CD25 and HLA-DR) after mitogen stimulation.

Dyskeratosis congenita is a rare, heritable, multisystem disorder, characterised by reticulate skin hyperpigmentation, mucosal leucoplakia, and nail dystrophy. More serious features are bone marrow involvement with pancytopenia and a predisposition to malignancy. Although the primary defect has not been identified, an X linked mode of inheritance has been shown in the majority of cases.[1] Recently, linkage in one large family by using X chromosome specific RFLP markers has assigned the gene for dyskeratosis congenita to chromosome band Xq28.[2] Several families with apparent autosomal forms of dyskeratosis congenita have also been reported, suggesting aetiological heterogeneity in this disorder.[3 4]

Chromosome breakage is not a consistent finding, although enhanced G_2 chromatid radiosensitivity has been observed in the fibroblasts.[5] This phenomenon has been observed in individuals genetically predisposed to cancer,[6] a characteristic also observed in dyskeratosis congenita. Patients with this disorder are also prone to opportunistic infections, and immunological abnormalities which include both humoral and cell mediated dysfunction. We report a case of dyskeratosis congenita with abnormalities in T cell subsets and impaired lymphoproliferative responses to in vitro stimulation with mitogens.

Case study

A 15 year old boy presented with characteristic dermatological features of dyskeratosis congenita which he had had since the age of 3 years. These included reticulate skin pigmentation, dystrophic nails, and oral mucosa leucoplakia. He had been immunised, including BCG, without complications. At the age of 10 years he had developed thrombocytopenia, which had progressed over the next few years to pancytopenia associated with bone marrow hypoplasia. At this stage a bone marrow transplantation was considered, but his parents refused consent. At the age of 15 he developed *Pneumocystis carinii* interstitial pneumonia, which was confirmed by the presence of protozoan cysts in the bronchial alveolar lavage. He responded to treatment with intravenous high dose co-trimoxazole. His male cousin (maternal side) was also similarly affected with dyskeratosis congenita, and died from sepsis at the age of 10 years.

His total white counts fluctuated from 6·4 to $0{\cdot}8\times10^{9}$/l, with absolute lymphocyte counts of 2·5 to $<0{\cdot}8\times10^{9}$/l. Serum immunoglobulin concentrations showed raised IgG 21·2 g/l, with normal concentrations of IgA 2·09 g/l, and IgM 2·1 g/l. HIV antibody was absent. Delayed hypersensitivity skin test to the purified protein derivative (10 unit dose) was negative, suggesting anergy.

Materials and methods

ISOLATION OF BLOOD MONONUCLEAR CELLS

Blood mononuclear cells (BMC) were prepared from heparinised blood by the standard Ficoll-Hypaque gradient.

CELL MARKERS

Cell surface expression of T cell subsets was assessed by indirect immunofluorescence using monoclonal antibodies against CD3, CD4, CD8 (Becton Dickinson). Half a million BMC were suspended in 100 μl Roswell Park Memorial Institute medium 1640 (RPMI-1640) supplemented with 2·5% fetal bovine serum and 0·01% sodium azide (staining buffer) and incubated with the respective monoclonal antibodies for 30 minutes on ice. This was followed by washing in staining buffer and a similar incubation with fluorescein isothiocyanate conjugated affinity purified goat antimouse immunoglobulin. The cells were then washed extensively and analysed using the FACScan flow cytometer (Becton Dickinson).

To assess the ability of T lymphocytes to express activation antigens upon stimulation with mitogen, cells were stimulated with phytohaemagglutinin 0·5 μg/ml. After a 48 hour incubation, the stimulated cells were stained separately with fluorescein-conjugated monoclonal antibodies against CD25 or HLA-DR, and phycoerythrin-conjugated CD3. The cells were read by two colour fluorescence analysis using the FACScan flow cytometer.

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Accepted 18 December 1991

Table 1 Expression of the T activation markers CD25 and HLA-DR, shown by percentage increase in these factors

	Control		*Patient*	
	CD3 CD25	*CD3 HLA-DR*	*CD3 CD25*	*CD3 HLA-DR*
Medium	11	8	15	17
PHA 12 5 μg/ml	98	25	92	25

PHA, phytohaemagglutinin

Table 2 Lymphoproliferative responses to mitogens

	^{3}H-thymidine incorporation (counts/min)			
	Expt 1		*Expt 2*	
	Control	*Patient*	*Control*	*Patient*
Medium	750	228	804	350
Phytohaemagglutinin	86 070	39 725	105 721	30 250
Concanavalin A	30 279	8 305	85 615	10 125

LYMPHOPROLIFERATIVE RESPONSES

Lymphocyte proliferative responses to the mitogens, phytohaemagglutinin (0·5 μg/ml) and concanavalin A (10 μg/ml) were assessed in microtitre plates containing 1×10^5 BMC suspended in RPMI-1640 supplemented with 10% fetal bovine serum, 2 mM L-glutamine and 100 U/ml penicillin and 50 μg streptomycin. Cells were pulsed with 1 μCi per well of tritiated thymidine (Amersham International) after 72 hours, and harvested 16–24 hours later using an automated cell harvester. Cell uptake of tritiated thymidine were then counted using a β scintillation counter (Beckman). Lymphocyte stimulation was assessed by the difference between the triplicate stimulated cultures and the unstimulated cultures measured in mean counts per minute.

Results

Evaluation of T cell numbers and subsets showed normal percentage of CD3 positive cells (76%). There was a reversal of CD4:CD8 ratio (which now measured 0·38), with percentages of CD4 and CD8 of 21% and 55%, respectively. The absolute numbers of CD4 positive cells were depressed ($0{\cdot}19 \times 10^9$/l; normal range $0{\cdot}25$–$1{\cdot}33 \times 10^9$/l), although the absolute numbers of CD8 positive cells were normal ($0{\cdot}50 \times 10^9$/l; normal range $0{\cdot}18$–$1{\cdot}18 \times 10^9$/l). Similar values were obtained on two other occasions. Although the lymphocytes were able to express the activation markers CD25 and HLA-DR after in vitro stimulation with phytohaemagglutinin (table 1), the lymphoproliferative response to phytohaemagglutinin and concanavalin A was impaired (table 2).

These results indicate the presence of impaired cell mediated immune responses in this patient with dyskeratosis congenita. This depression is likely to be contributed by the reversal of the CD4:CD8 ratio and the decrease in absolute numbers of CD4 positive cells. The ability of the patient's T cells to express activation markers upon mitogen stimulation suggests an intact T cell activation pathway.

Discussion

Dyskeratosis congenita is a genetic condition which is ultimately lethal. We have previously reported the characteristic mucocutaneous features in two of our local patients with this disease.[7] Abnormalities in immune function in this disorder is evidenced by a high incidence of unusual infections, and the primary causes of death are infections and carcinoma. In this study, our patient with dyskeratosis congenita and depressed cell mediated immunity developed interstitial pneumonia due to *P carinii* infection; this is an opportunistic infection usually affecting patients with depressed T cell function.

There have been other reports of abnormalities of cell mediated immunity in dyskeratosis congenita. These have included absence or delayed hypersensitivity to a battery of skin test antigens,[3] and impaired response to mitogenic stimulation upon in vitro testing.[8] Our patient also showed impaired lymphoproliferative responses to in vitro stimulation with mitogens (table 2). The mechanism for the impaired cell mediated function has not been delineated. As shown in this study, the presence of a markedly depressed CD4:CD8 ratio (0·38) and decrease in absolute CD4 positive cells are likely contributing factors. The T cell activation pathway appears to be intact since the patient's T cells were able to express normally the activation marker CD25 and HLA-DR (table 1). Expression of these receptors upon lymphocyte activation are an important feature of cellular immunity, as abnormalities in their expression have resulted in severe combined immunodeficiency syndrome.[9 10]

There have also been reports that suggest abnormalities of humoral immunity in patients with dyskeratosis congenita. A wide range of immunoglobulin abnormalities have been reported, including diffuse hypoglobulinaemia,[11] decreased IgG and IgM with normal IgA,[8] normal IgG and IgA with slightly decreased IgM,[12] and increased IgG.[13] Our patient had hypergammaglobulinaemia. With the presence of cell mediated abnormality, as seen in our patient, it is tempting to postulate that the dysgammaglobulinaemia may result from abnormal T cell help, similar to that seen in paediatric acquired immune deficiency syndrome.[14] Interestingly, the genes for dyskeratosis congenita and X linked severe combined immunodeficiency, a condition also associated with depressed cellular and humoral immunity, have both been located on the long arm of the X chromosome. Their locations on the long arm of the X chromosome differ, with the former located in the Xq28[2] band and the latter between region Xq13.1 and Xq21.1.[15]

This study was supported by National University of Singapore Research grants RP 880369 and RP 880337

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Anal abnormalities in childhood myotonic dystrophy—a possible source of confusion in child sexual abuse

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Abstract

Myopathic involvement of the perianal musculature is one of the less well recognised features of myotonic dystrophy in children and may present with physical signs suggestive of sexual abuse. Details of six children with myotonic dystrophy are presented to emphasise the importance of considering an underlying myopathic condition in the differential diagnosis of anal laxity.

Involvement of smooth, as well as striated, muscle in the pathological processes of myotonic dystrophy is well recognised and may give rise to important symptoms, especially when involving the oesophagus or colon.[1] [2] Abnormalities of anal sphincter and rectal pressure, documented in adult patients with myotonic dystrophy, are likely to reflect such pathological changes in the external and internal anal sphincter muscles.[3] [4] The interplay of several pathological mechanisms, including muscle atrophy, myopathy, and neural disturbance is suggested as the basis of these anal sphincter changes by studies in adult patients with myotonic dystrophy.[5] The present report suggests that similar changes may also be observed in children, in whom awareness of the possible implications of anal abnormalities may raise the suggestion of sexual abuse.

After recent referral of a child with the congenital form of myotonic dystrophy and anal abnormalities, in whom the possibility of sexual abuse had been inappropriately suspected, we have reviewed the extensive records of children with myotonic dystrophy available to this department, and identified other instances of anal abnormalities in this patient group. We are aware of approximately 200 children with this muscle condition. However, clinical data are lacking in many instances as the family may have come to attention for DNA testing or advice on a particular clinical issue and not have been seen here. For these reasons it is difficult to quantify the patient base from which these other five cases have been drawn.

By emphasising the nature and range of these anal abnormalities, we hope to alert colleagues to this important muscular cause of anal sphincter dysfunction and so avoid confusion with anosexual abuse and the distress that related investigations will cause to families.

Case reports

Case 1 was a 14 year old girl with congenital myotonic dystrophy that had been diagnosed when she was 1 year old and had been referred for investigation of developmental delay. Her mother, in whom classical features of the adult form of the disease were observed, was also diagnosed as having the disease. The main features of the patient's condition were developmental delay, recurrent ear infections, and orthopaedic problems stemming from bilateral talipes at birth. Bowel habit was generally regular and her intermittent episodes of constipation were satisfactorily treated with laxatives.

During the course of a sex education class at the special needs educational establishment that she attended, the patient claimed to her teacher than she had had sexual relations with a male member of her family. Although this was not considered by staff or others to have a serious basis, there followed an investigation by a joint social services and police investigation team. Genital examination by this team showed no evidence to substantiate her claim. However, concern was expressed at her abnormally lax anus, which was felt by the police surgeon to be unrelated to her underlying muscle condition and more likely to be indicative of insertion of an object into the patient's anal canal. At examination the anal sphincter was dilated and floppy with faeces clearly visible in the rectum. A reflex dilation of the anus was

Details of history and clinical signs in cases 1–6

Case No	*Sex*	*Age at presentation (years)*	*Presenting history*	*Attempted management*	*Anal signs*
1	F	14	Intermittent constipation	Laxatives	Anal sphincter laxity, reflex dilatation
2	F	15	Lifelong faecal soiling	—	Appreciable anal sphincter laxity (figure)
3	M	18	Episodic diarrhoea	Behaviour modification	Anal sphincter laxity, anal margin inflammation
4	F	12	Daily incontinence	Loperamide and metoclopramide	Anal laxity
5	M	8	Episodic incontinence	Dietary	Anal sphincter laxity, anal margin inflammation
6	F	8	Occasional incontinence	Behaviour modification, loperamide	Anal sphincter laxity, perianal inflammation

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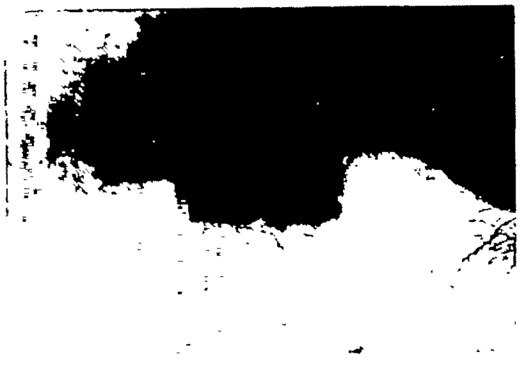
Accepted 22 November 1991

(*Arch Dis Child* 1992;67:527–8)



Anal sphincter laxity in case 2.

observed on parting the buttocks. After confirmation that similar features had been observed in other children with myotonic dystrophy, the investigation was closed and the male family member fully exonerated.

Details of five other cases are presented in the table; anal sphincter laxity for case 2 is shown in the figure.

Discussion

The interpretation in children of physical signs consistent with sexual abuse is a difficult area for clinicians. Moreover, the distressing consequences for families of misinterpretation of physical signs as evidence of sexual abuse demand that any such signs as do exist are accurately interpreted. While it is acknowledged that a significant number of sexually abused children have no abnormal physical findings, there is also a recognition that very few signs are diagnostic of abuse.[6] In view of our ignorance of the pathophysiology of the anal canal, it is especially difficult to weigh the significance of anal signs in relation to possible sexual abuse.[7]

This report highlights anal signs of sphincter laxity, reflex anal dilatation, perianal inflammation, and faecal soiling in children with myotonic dystrophy and underlines the significant management challenge that attends these problems. A diagnosis of sexual abuse was entertained in two cases, leading in both to a social services and police joint investigation, with obvious distress to the families involved. In both instances the weight of evidence in favour of sexual abuse revolved around the anal signs.

The uncertainties inherent in interpreting the physical signs of sexual abuse are readily acknowledged, as is the principle that such examination and interpretation will be best performed by those with a particular expertise in the field. However, in view of the physical signs reported in this series of patients, a useful caveat to those charged with so onerous a responsibility might be to beware of the possibility of misleading anal signs in children with unexplained developmental delay and in conditions which can lead to disturbances in muscle tone. Recognition of these alternative causes of anal abnormalities may help avoid the trauma of sexual abuse investigation in some families.

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Sonographic detection of the lead point in intussusception

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Accepted 21 November 1991
(*Arch Dis Child* 1992;67:529–30)

Abstract

Using ultrasonography, a caecal duplication cyst was identified as the pathological lead point in a 6 year old boy with acute intussusception. The patient underwent definitive surgery rather than inappropriate treatment by attempted radiological reduction. Various pathological lead points in intussusception can now be defined by ultrasound.

Most cases of childhood intussusception are secondary to lymphoid hyperplasia in the terminal ileum but in as many as 10% of patients a more definite pathological lead point, such as a Meckel's diverticulum, small bowel tumour, or duplication cyst, is responsible.[1] Such patients are at risk of recurrent intussusception and other complications of the underlying pathology and therefore should be treated surgically rather than by radiological reduction methods. In recent years ultrasonography has emerged as a useful diagnostic aid in intussusception. We believe that the role of ultrasound extends beyond that of confirming the diagnosis. It can also be used in some cases to identify pathological lead points, thus enabling simpler and safer management of the patient. This is exemplified by the following unusual case report.

Case report

A previously well 6 year old boy was admitted with a two day history of colicky abdominal pain and bile stained vomiting. On examination he appeared well without signs of dehydration and had a non-tender mass palpable in the epigastrium. Plain radiography suggested a soft tissue mass in the right upper quadrant of the abdomen. Ultrasonography (5 MHz sector and 7·5 MHz linear probes with the commercially available ALOKA 280LS scanner) confirmed the clinical diagnosis of intussusception but also demonstrated a 4 cm cystic lead point in the transverse colon (fig 1). Consequently, pneumatic reduction was not attempted and the patient was prepared for a laparotomy.

At operation, a caecocolic intussusception was reduced, revealing a 4–5 cm cystic lesion within the caecal wall. The caecum and appendix were excised and intestinal continuity restored. The patient made an uncomplicated postoperative recovery and has remained well. Histology demonstrated a caecal duplication cyst lined by large-bowel mucosa.

Discussion

Ultrasonographic identification of a pathological lead point in this patient avoided an inappropriate attempt at radiological reduction. If such an attempt had succeeded, the child would have been exposed to the risks of recurrent intussusception and other potential complications of the duplication cyst. The cyst is unlikely to have been detected during a pneumatic reduction judging by the reported experience of similar lesions with barium enemas, which often provide even better radiological definition.

We believe that ultrasonography is underused in the management of childhood intussusception. During the past two years we have used both ultrasonography and contrast enemas to confirm

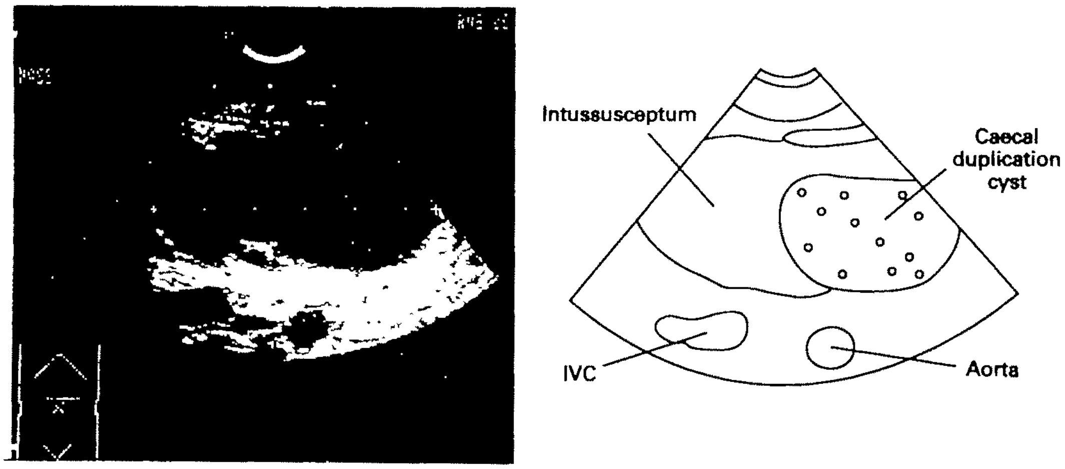

Figure 1 Longitudinal section of cystic lead point at the apex of the intussusceptum in the distal transverse colon (5 MHz sector probe); IVC=inferior vena cava.

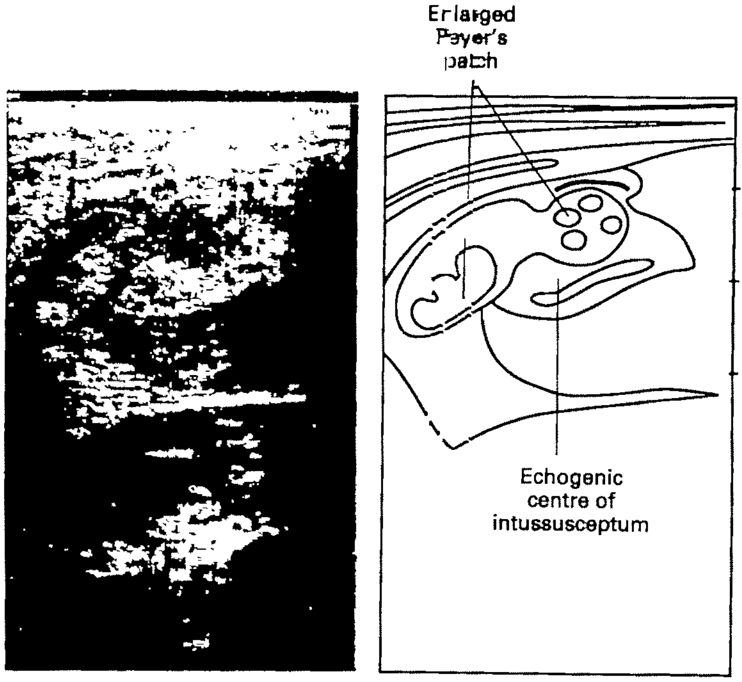

Figure 2 Typical discrete lesion (enlarged Peyer's patch) seen in transverse section at the apex of an 'idiopathic' ileocolic intussusception (7.5 MHz linear view)

or exclude intussusception in children not obviously requiring surgery, and our experience accords well with that of Pracros *et al* who found ultrasonography safe and reliable with neither false positives nor negatives.[2] However, clearly the experience of the sonographer is important and if the diagnosis of intussusception remains uncertain after scanning with ultrasound, contrast studies should be performed.

There are several reports of children with other pathological lead points detected by ultrasound, including Meckel's diverticula[3] and a small bowel lymphoma.[4] One child with a false cystic lead point due to encysted fluid within the intussusception has been described but the appearances differ from our case.[5] In some patients we consider that it has been possible to identify the lymphoid hyperplasia of 'idiopathic' intussusception within the intussusceptum (fig 2). Yet another diagnostic role of ultrasound is in the detection of small bowel intussusception which often proves difficult with conventional radiology. Reported examples include ileoileal intussusception occurring postoperatively[4] and in Henoch-Schönlein purpura.[6]

In summary, not only is ultrasonography able to accurately diagnose intussusception, including the more difficult small bowel intussusception, but it may also be used to define a pathological lead point as demonstrated by this case report. This contributes to safer and simpler patient management.

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Tuberculin skin reactivity four years after neonatal BCG vaccination

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Abstract

Two hundred and sixty one of 279 (93·5%) children known to be tuberculin positive shortly after receiving their neonatal BCG vaccination were still tuberculin positive at age 4 years. The results confirm the continuing effectiveness of neonatal BCG at 4 years.

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Accepted 29 July 1991

(*Arch Dis Child* 1992,67:530–1)

Grindulis *et al*[1] found a surprisingly low percentage of children to be tuberculin positive at age 22 months after neonatal BCG vaccination.[1] A survey of tuberculin reactivity six to nine weeks after BCG vaccination confirmed very high effectiveness.[2] A proportion of the children from that survey had their tuberculin reactivity retested at age 4 years.

Subjects and methods

Altogether 863 infants whose ethnic origin was the Indian subcontinent and who were born between August 1984 and July 1985 were tuberculin tested six and nine weeks after neonatal vaccination.[2] A total of 846 (97·3%) were positive grades 1 or 2. A random one third of tuberculin positive infants from each month (totalling 279) had their skin tuberculin test (tine test, Lederle) repeated at the age of 4 years.

Results

Of the 279 children who had grade 1 or 2 positive tuberculin tests in 1984/5 tested, 18 (6·5%) were tuberculin negative and 261 (93·5%)

were tuberculin positive. Altogether 251 of the 261 tuberculin positive results were grades 1 or 2 consistent with the BCG vaccination history. Ten had increased tuberculin reactions grade 3 or 4. Further investigation showed additional factors in these cases, such as household or non-household contact with tuberculosis.

All 10 of the children with grade 3 or 4 positive tests have been given chemoprophylaxis because of their contact history or after extended visits to the Indian subcontinent with strongly positive tests on return.

Discussion

This study shows a continuing high tuberculin positive rate at age 4 years in those who were shown to be tuberculin positive six to nine weeks after receiving their neonatal BCG. Crawshaw and Thompson also showed 19/22 (85%) of children to be tuberculin positive between 42 and 60 months.[3] An appreciable proportion of children from the Indian subcontinent (80/103, 77·6%) were still tuberculin positive at age 12 when retested for the school programme.[4] Our initial results showed a 97·3% rate of tuberculin positivity at six to nine weeks,[2] and 93·6% of the neonates tuberculin positive at six to nine weeks were still tuberculin positive at age 4 years. Packe and Innes showed both a 95% positive tuberculin test rate after vaccination at age 3 months and a 65% overall protective effect.[5] Hadfield *et al* showed a 97·8% positive rate after neonatal vaccination with a Dermojet injector.[6] Thus three separate series found tuberculin positive rates between 95–97% after BCG vaccination in the first few months.[2,5,6] This study supports earlier small studies showing a substantial tuberculin positive rates four to 12 years after vaccination.[3,4] A negative tuberculin test does not mean that the vaccination is ineffective, however, as the degree of protection conferred on the individual is independent of the degree of tuberculin skin sensitivity induced.[7]

This study in children already shown to have been tuberculin positive shortly after the initial vaccination refutes the findings of Grindulis *et al*.[1] The explanation for the discrepancy between the results is that we were able to show an initial tuberculin response due to effective vaccination. As a quarter of the patients of Grindulis *et al* had no BCG scar, the likely explanation is not a failure of the vaccine but of failure of the vaccination technique.

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Association of high fever and short bacterial excretion after salmonellosis

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Accepted 17 December 1991

(*Arch Dis Child* 1992;67:531–2)

Abstract

One hundred and two children with salmonella gastroenteritis were studied for factors affecting the length of convalescent bacterial excretion. There was a significant correlation between degree of fever and duration of excretion: a fever of ≥40°C had the shortest and no fever the longest duration of excretion. Fever therefore appears to have a favourable prognostic influence on the length of salmonella excretion.

Excretion of salmonella is an important public health problem that requires considerable attention and resources in countries with good hygienic standards.[1] Factors associated with prolonged excretion of salmonella include malnutrition, use of antibiotics, young age, symptomatic infection, and infection with salmonella other than *Salmonella typhimurium*.[2,3]

Accumulating evidence suggests that fever is beneficial to the infected host.[4] A recent study of 125 children with salmonella gastroenteritis admitted consecutively to Ahmadi Hospital in Kuwait showed that children with a temperature greater than 40°C had a significantly shorter duration of bacterial excretion compared with afebrile children (AS El-Radhi, unpublished data). The aim of this study was to determine whether the same observation holds for Finnish children with salmonella gastroenteritis.

Patients and methods

The case records of all children who were hospitalised at the paediatric department of Aurora Hospital, Helsinki, Finland, with acute gastroenteritis and a positive stool culture for non-typhoid salmonella were reviewed. The children were consecutive admissions with acute illness during a period of 17 years (January 1974 through December 1990). The study group consisted of 102 children (54 boys and 48 girls) aged less than 16 years (mean age 5·6 years; range 3 months–15·5 years). Children whose illness commenced in foreign countries or who were referred to the hospital after the diagnosis had been established were not included. Temperature was recorded on admission and every four hours in the hospital. In children 5 years of age and under the temperature was measured rectally for three minutes and in older children axillary for seven minutes. Usually paracetamol 10 mg/kg every four hours was prescribed for fever above 38·5°C. None of the children received antibiotics specifically aimed at salmonella infection. Nine children received penicillin and six other children received various other antibiotics at the acute stage of illness. Routine investigations included a full blood count, measurement of concentrations of serum electrolytes, urea, and C reactive protein, and bacterial cultures from stool and urine. Blood culture was performed if clinically indicated. After discharge, a weekly stool specimen was submitted to the Epidemiological Department, City of Helsinki, until a bacteriological cure was achieved, defined as at least three successive negative cultures. The duration of excretion was assessed with the accuracy of one week.

The following measures of fever were considered in the analysis: temperature recorded on admission, the highest temperature recorded in hospital, and the highest mean temperature (usually a mean of four recordings) on any day in hospital.

Results

There was a weak but significant correlation between the age and the duration of bacterial excretion ($p<0·05$), $r=-0·21$), with younger patients having a longer duration of excretion.

The salmonella isolates consisted of 60 cases of *S typhimurium*, 18 cases of *Salmonella enteritidis*, and 24 cases with other salmonellae. The mean (SD) duration of excretion was 5·4 (6·2) weeks for *S typhimurium*, 3·8 (3·7) weeks for *S enteritidis*, and 5·4 (13·6) weeks for other salmonellae; these differences were not significant ($p=0·3338$, analysis of variance using logarithmic transformations of duration of excretion).

There was a significant association between the degree of temperature, whether on admission, highest ever, or the highest mean temperature on any day recorded in hospital, and the duration of excretion ($p=0·0004$, analysis of variance for each of the measures of fever).

Fever on admission and duration of bacterial excretion after salmonella gastroenteritis in children

Degree of fever	*No of children*	*Duration of salmonella excretion (weeks)*			
		Range	*Mean*	*Mean (SD)*	*Mean (SD)* of log (1+x)*
(A) ≥40°	15	0–10	0	1·9 (2·9)	0 301 (0 363)
(B) 38°–39·9°	66	0–18	3	4 1 (4·0)	0 585 (0 339)
(C) ≤37·9°	21	2–60	7	11 7 (15 1)	0 912 (0·383)

*F=13 70, p=0 0001, analysis of variance (log (1+ duration of excretion)) Pairwise comparisons with Tukey-Cramer test: (A) *v* (B), p=0 0160; (B) *v* (C), p=0 0011, (A) *v* (C), p=0 0001

Considering the degree of temperature on admission, the 102 patients were divided into four groups: (i) a temperature of ≥40°C (n=15), (ii) a temperature of 39–39·9°C (n=22), (iii) a temperature of 38–38·9°C (n=44), and (iv) no fever at presentation and a normal temperature during hospitalisation (n=21). When these groups were compared with each other for the length of bacterial excretion no difference was found between groups (ii) and (iii); these were pooled to make a group of 66 children with fever from 38–39·9°C. A comparison of the three remaining groups is presented in the table. The mean excretion time of salmonella was shortest in children who presented with fever of ≥40°C and longest in those who were afebrile at presentation.

No correlation was found between the leucocyte count or concentration of C reactive protein and the duration of bacterial excretion (data not shown).

Discussion

Several factors are known to influence the clinical course and the duration of bacterial excretion after salmonella gastroenteritis.[2 3] In this study a tendency towards longer duration of excretion was seen in younger children; this finding is in agreement with other studies.[1]

In our study a significant correlation was found between the duration of convalescent excretion and fever at the initial stage of illness. The shortest mean duration of excretion was found in children with high fever on admission and the longest was in afebrile children, including all four children who continued to excrete for longer than six months. Although the reason for this finding is not clear, there is evidence from human and animal studies suggesting that fever as a response to infection is beneficial to the infected host in accelerating the local inflammatory reaction and limiting the spread of infectious agent.[5] Fever enhances cytokine production leading to a higher production of antibodies and cell proliferation aimed at combating the invading organisms.[6]

In conclusion, our data suggest that fever may be a useful sign in children with salmonella gastroenteritis in predicting short duration of salmonella excretion after acute illness. Afebrile and young children may have a short and uncomplicated clinical course of illness but a prolonged bacterial excretion.

We thank Ms Tuija Poussa for statistical analysis.

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Archives of Disease in Childhood 1992; 67: 533–535

STATISTICS FROM THE INSIDE

5. Data structures

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The appropriate statistical analysis and interpretation of a set of data depend critically upon its *structure* in terms of statistical dependence and independence. If for instance there are two populations to be compared, the samples from them may be drawn independently or they may be paired or matched. In the latter case a reading in one of the samples tells us something about the value of its mate in the other sample, and the two samples cannot be considered independent.

The data structure will depend mainly upon the manner in which the data have been collected. It is not possible to provide an adequate statistical analysis of a body of data unless the method of collection is thoroughly understood—one of several arguments for invoking statistical thinking, professional or otherwise, *before* the data collection takes place.

Paired and unpaired data

The most familiar structural distinction is that outlined above—when it is required to compare two populations, the sample items may either be matched or independent. The distinction is usually obvious, but it can be checked by seeing whether the items in one sample can be sensibly written down in a different sequence while keeping the other sample fixed; if this is not so, some kind of matching must be involved.

In both these two structures (assuming a continuous measurement-type variate is in question) the quantity of interest is the difference between the population means. The usual methods of analysis are the paired and unpaired *t* analyses. With matched pairs of items, the two populations give rise to a single population consisting of differences between pairs of items. The difference between the means of the original populations is equal to the mean of this population of differences. The mean and standard deviation of this latter population can be estimated using the differences obtained from the sample. The estimated standard error of the mean difference can thus be calculated, and the analysis proceeds in a straightforward manner along the lines described in note 4 to produce a significance probability and confidence limits.

Note that the presentation of the results from paired samples should relate to the population of differences, so that it is essential to present the sample mean difference with its standard error; the standard deviations of the two original matched samples are of little relevance and can usually be omitted. If the original data are to be plotted in a figure, the members of each pair must be joined by a line; alternatively, a plot of the differences can be given.

When the two samples are not matched, the tactic of forming differences is not available. Instead, recourse can be had to the only piece of mathematical statistics that is worth committing to memory:

> *The variance of the difference between two quantities which are statistically independent is the sum of their individual variances.*

(The simplicity of this result explains why so many statistical techniques are more easily explained in terms of variances than of standard deviations.)

Because the two samples have been drawn independently from their populations, the two sample means are statistically independent. Accordingly, the variance of their difference is the sum of their individual variances and this can be written as

$$\frac{\sigma_1^2}{n_1}+\frac{\sigma_2^2}{n_2}$$

where σ_1^2, σ_2^2 are the variances of the two populations and n_1, n_2 are the sample sizes. The standard error of the difference will be the square root of this.

At this point it is usual to make the further assumption that the two population variances are equal (even if the means are not). This is plausible enough in the context of significance testing at least; it seems a bit far fetched to assume as a null hypothesis that the two populations have identical means but different standard deviations. It is possible to make a formal significance test of the assumption by calculating the ratio between the sample variances. This ratio is always referred to as *F* (for Fisher) and tables are widely available from which the significance probability corresponding to a given value of *F* (and the two sets of degrees of freedom) can be obtained. This is actually not at all a good idea. There are three reasons for this:

(1) Logically, it is a misuse of a significance test. The test may throw doubt upon the null hypothesis of equal variances if the significance probability is small, but it does not establish the null hypothesis in the contrary situation—'not significant' *never* implies 'non-existent'. Furthermore, the *F* test in this context (though the best test available) is not very powerful unless the samples are large. This means that it is likely to have a fairly high type II error rate—even when the true variances are noticeably different, the probability of not obtaining a significant value of *F* may be quite substantial.

(2) Unlike the *t* test, the *F* test for the

equality of variances relies heavily upon the Normality of the two distributions. With data from quite mildly non-Normal distributions, the actual significance probability may be quite far from that in the tables. Usually in practice, the results will appear to be more significant than they actually are.

(3) The assumption is anyway not one of critical importance. The t test is *robust* to the assumption of equal variances, in the sense that even when the assumption is false, the tabulated significance probabilities will not usually be far from the truth.

In summary, unless the sample variances are very different (by a factor of 5 or more, say) the assumption of equal variances can usually be made safely If the variances do differ markedly, a different method of analysis will be required. This may involve transformation of the data, perhaps to a logarithmic scale, and this will be the subject of a subsequent note in this series.

The point of assuming a common population variance is that both sample variances are now estimating the same thing. They can thus be combined into a single estimate which will be more precise than either one taken separately. The method of doing this is quite simple; the sum of squares of deviations from the mean and the degrees of freedom are calculated for each of the samples and the total of the two sums of squares is divided by the total of the two degrees of freedom (the divisor (n_1+n_2-2) which appears in many textbooks is actually $(n_1-1)+(n_2-1)$). This procedure is known as *pooling* the two estimates. Note that it is equivalent to forming a *weighted mean* of the two sample variances using the degree of freedom as weights.

Given the pooled estimates of variance, s^2 say, the analysis of unpaired data is straightforward. The variance of the difference between the means is given by $\sigma^2(\frac{1}{n_1}+\frac{1}{n_2})$. This is estimated by $s^2(\frac{1}{n_1}+\frac{1}{n_2})$, and the square root of this quantity provides the estimated standard error of the difference. This standard error can be used along with values of t having $(n_1-1)+(n_2-1)$ degrees of freedom to provide significance probabilities and confidence intervals for the difference between the population means.

In presenting the results from unpaired data, the individual means and standard errors of the two samples are now of more relevance as the difference of the means and its standard error can be obtained from them, but it will help the reader if these derived quantities are shown explicitly. Thus part of a results table might read

Means (SEs)		
Treatment (n=16)	Control (n=25)	Difference (T−C)
2·54 (0·25)	2·87 (0·20)	−0·33 (0·32)

Analysis of variance

The notions of paired and unpaired structures extend readily to comparisons involving three or more populations. Such comparisons may be based upon independent samples, or they may utilise matched sets or blocks of three or more items as appropriate. The related methods of analysis are respectively one way and two way analysis of variance. These methods are not as complex as is sometimes thought, and they are widely available in computer packages. It is again important to use the method which is appropriate to the actual structure of the data. If carefully matched data are analysed using a one way analysis of variance (which ignores the matching), the resulting estimate of error is likely to be too large; the work involved in the matching is wasted and the conclusions from the data will be unnecessarily imprecise.

In the present context, analyses of variance are best thought of simply as arithmetic devices for providing a single estimated error variance which can be used when comparing the means of the different groups. They do also provide an F value which is the ratio between the variance derived from the group means and the error variance. This tests the null hypothesis that *all* the population group means are equal. The usefulness of this is limited by the fact that there is no associated estimation procedure—a significant value of F suggests to us that the means are different without giving any information about the sizes or pattern of the differences. For interpretation, the analysis of variance table almost always needs supplementing with suitable tables of means and standard errors. The view sometimes put forward that t tests between individual pairs of means must not be made unless the overall value of F is significant at some level is far too simplistic to be useful.

One way analysis of variance is especially simple as it involves little more than pooling the sample variances of the different groups in exactly the same way as when two populations are concerned. Pooling may be more important, though, as variance estimates from several small samples, each one too imprecise to be very useful on its own, can be pooled to provide a single estimate of reasonable precision. Data with this structure are sometimes analysed using unpaired t tests on every pair of means. This necessarily involves the assumption that all the population variances are equal, so that it is wasteful of information not to use the single pooled estimate. As in the case of two populations, departures from the assumption of equal variance are usually not of great practical importance, unless they are systematic; if, consistently, groups with the larger means also tend to have the larger variances, transformation of the data may be advisable.

Analyses of variance can of course be calculated when there are only two populations in the dataset, the situation more usually handled by calculating a value of t. It is not always appreciated that the two analyses are exactly equivalent. The numerator of the F ratio provided by the analysis of variance has 1 degree of freedom, and the value of F is then *exactly* equal to the square of the corresponding value of t from the alternative type of analysis. The implication of this is that F ratios with 1 degree of freedom in the numerator should almost never be quoted; in the background there must be a mean with its estimated standard error, and quoting these instead will be far more informative.

A very difficult problem that arises when there are more than two populations to be compared stems from the number of possible comparisons that can be made. Suppose, for example, that there are four groups in an experiment, labelled A, B, C, and D. These give rise to six possible comparisons between pairs (AB, AC, AD, BC, BD, and CD), and there are further comparisons that may be of interest—if group A are controls, for example, we may wish to compare the mean of group A with the mean of the other three groups taken together. For each individual comparison we can control the type I error rate at (say) 0·05 by using an appropriate value of t in the significance tests, but the probability that at least one of the six or more comparisons will reach significance by chance alone will be considerably greater than 0·05. This is the problem of ***multiplicity*** and in my view has no logically satisfactory solution. There exist a number of ***multiple comparison*** procedures which aim to reduce the type I error probability to a specified level for all the possible comparisons taken together, but the only way to do this is to increase the value of t to some extent so that the type I error rate for any single comparison is less than 0·05. The inevitable consequence is that the type II error rate is increased. In a sense, the more groups there are in the experiment, the less likely is the detection of a real difference between the groups. It has, I think, to be faced that the more statements you make, the more likely it is that you will be mistaken; or, put another way, the only people that make no mistakes are those who never say anything.

Archives of Disease in Childhood 1992; 67: 536–542

TYPES OF PSYCHIATRIC TREATMENT

Counselling parents in child behaviour therapy

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This is the third of a series of articles on treatment of child psychiatric disorders.

Over the past 21 years the field of behaviour therapy with children has expanded considerably. Ollendick cites a 1968 report by Gelfand and Hartman in which only 70 studies relating to child and adolescent behaviour therapy could be found in the literature.[1] By 1981 this figure had expanded to 1000. This growth has continued and so much so that it is now difficult for the practising clinician to keep abreast of developments within the now extensive literature.

In the late 1960s behaviour therapy was characterised by two main approaches. Directly from the principles of operant conditioning, reinforcement procedures were developed for increasing and decreasing behaviour and these found favour mostly in the fields of mental handicap and conduct disorders. The other approach derived its strategies from classical or respondent conditioning and, in the main, included desensitisation techniques and these were used most often to treat children with phobic and emotional disorders.

In the 1970s interest in imitation learning expanded the behaviour therapist's repertoire through the development of a new set of procedures collectively referred to as 'social skills training' Finally, the late 1970s and 1980s saw the development of a set of techniques deriving from an interest in cognitive processes. Included among these are self control techniques, self instructional training, coping and problem solving strategies, and approaches for the reversal of dysfunctional thinking. Though these latter procedures have seen use with wide groups of child problems, they have not, as yet, been satisfactorily validated in their use with overt clinical disorders.

One thread running right through the development of child behaviour therapy has been the idea that therapists, rather than treating the problems exhibited by children, should educate the parents into this role. Inherently, this makes good sense as it is the parents who have the maximum 'therapeutic' contact with their children. The approach, which is often referred to as 'parent training', has enjoyed enormous success and attention, and especially so in the fields of conduct disorder and mental handicap. Traditionally, hallmarks of this approach include: (i) careful family assessment through interviews and observations of parent-child interactions: (ii) training parents to monitor and track child behaviour; (iii) educating parents in reinforcement principles and a range of allied techniques, such as differential reinforcement, time out, contingency contracting and how to use point incentive systems; and, finally, (iv) teaching parents to generalise their successes across behaviours and over time. In this paper the author examines some of the issues relevant to each of these steps but, in particular, discusses aspects pertinent to the busy clinicians in routine practice.

When consulted about child behaviour problems, such as tantrums, sleep difficulties, disobedience and aggressiveness, it is often tempting to jump quickly to advice about firm, consistent management. However, between complaint and successful resolution, several aspects of our approach will influence the likelihood of success. Firstly, our methods of assessment and consequent understanding of the individuals, interactions, and developmental issues may suggest factors other than the actual consequences, which also require therapeutic attention. Secondly, as therapists the way in which we interact with the family will in many instances influence the treatment outcome. Thirdly, the manner in which treatment techniques are imparted will affect their utilisation, and finally, experience in the sorts of 'road blocks' that may hinder treatment progress will be important. Some aspects of each of these issues is discussed below.

Assessment of child behaviour problems

A basic prerequisite to any treatment advice is an understanding of the behavioural problems, their antecedents, and consequences.

BEHAVIOURAL ANTECEDENTS

Traditionally, parent trainers have concerned themselves with what is observable, and through this have demonstrated a number of immediate and frequently occurring problem antecedents. These include vague instructions, frequently repeated instructions, inconsistency in approach to the behaviour, failure to attend to prosocial behaviour, and attention to disruptive behaviour and sequences typified by escalating anger and aggression.[2] The ramifications for treatment obviously include teaching the parent to observe more accurately, issue clearer and fewer instructions, and to act earlier and more efficiency. However, this focus on immediate antecedents is often only part of the story.

The immediate interaction between parent and child is influenced by a wide range of events, including other interactions, the effects of family and environmental stressors, and the attitudes and beliefs that parents hold about child behaviour. Failure to attend to these will at worst result in unsuccessful treatment. On the other hand, careful consideration may suggest other and more appropriate approaches to treatment. Some of these aspects are discussed further.

Marital problems may lead to serious disagreements about child management, less time for the child, and impose additional stress upon the child.[3] In the face of open conflict, child management advice is ill advised until such difficulties are resolved or resolving. Perhaps though, in dysfunctional marriages characterised by apathy and disinterest, advice to one parent may have beneficial effects. Problems between parents may also be expressed in more covert ways. For instance, the child who sleeps with a parent may serve to mask parental sexual difficulties. One way to test such a hypothesis is to question parents about the consequences for them of successful child problem management. Other family interactional influences may present more subtly, and only became appreciated through careful investigation. Grandparents, for instance, may criticise and undermine parental efforts. This can often be managed either by appropriate parental assertion, ignoring, or at worst by grandparent exclusion. Finally, siblings who while not perceived as problematic, nevertheless often exhibit some problems and therefore may require to be included in treatment.[2] More subtly, if labelled 'good', such children may, in maintaining their relative position, persist in covertly provoking the labelled child. In such cases, if intersibling fighting is problematic, then parents may be best advised to ignore fighting in order to avoid being dragged into a 'good'/'bad' labelling game.

Families may be exposed to a range of stressors that have detrimental effects on child rearing. It has been established that in the year or so after parental separation, mothers may have management difficulties especially with their sons.[4] Here, rather than focusing intervention on child management, it may be far more appropriate to support and advise the mother with regard to the enormous adjustment she is having to make. Other stresses, such as parental depression, illness, or child illness, also require appropriate consideration before child management advice is contemplated.

An inquiry into parent day to day coping may reveal ways in which child difficulties can indirectly be alleviated. At the simplest level for instance, adjustments in parents' daily timetable can create more space and thus reduce stress around areas of child management. For example, in one of the author's cases, a young mother habitually attempted to dress three young children, make breakfast, get them out to school, and complete some household tasks—all in the space of one hour. In situations where organisation is more chaotic, then various problem solving and coping skills strategies may be required.

Multiproblem families pose the greatest challenge for parent trainers. Not only are they multistressed, but also they frequently exhibit a broad range of poor coping skills. Also it is often assumed that they are deficient in parenting skills. However, this is not usually the complete story. Research has demonstrated that these parents can 'learn' and successfully use behavioural management techniques, but unfortunately such improvements are often not maintained.[5] It would appear that their problems lie more within dysfunctional attributions and expectations about their children and their life circumstances. In any case, efforts to improve child management in such families will at least require prolonged and diverse treatment.

In the early days of parent training an implicit assumption that attitude change would follow behaviour change existed. This was a naive generalisation. At initial interviews, one is often struck by the strength of parental belief statements such as, 'I've tried everything and nothing works', 'He's just like his father', 'He doesn't learn', etc. No doubt, in milder cases, direct behavioural advice with successful application may extinguish these beliefs. However, in more difficult cases the belief may hinder progress from the beginning. Take for example, a mother who feels that nothing works, thinks she is a bad parent, and sees her child as failing to learn, and consider how she approaches her child when trying to get him to bed. She is likely to feel fed up and/or angry, and in consequence her approaches to the child will often convey a lack of belief in her own management ability. Frequent failure will reinforce such dysfunctional beliefs, and perhaps also lead to inconsistency of effort and rule application. Also, other adults may reinforce the beliefs either by taking over the management, or more directly, by criticising the mother. If the therapist is to avoid failure, then some preliminary work with dysfunctional beliefs will often be necessary. Basically, such will involve identifying the beliefs, teaching the parent to monitor them, then learning to examine them according to reality and finally, in consequence, learning to establish more appropriate ones in their place. For example, if the parent considers that 'nothing works', then an in-depth examination of behavioural incidents to which this is linked is required. Often this will reveal that what was thought not to work, was not in the first instance applied appropriately. Equally, other behavioural incidents will illustrate that the techniques appropriately applied did work. In cases where dysfunctional thinking is intense and associated with significant emotional distress, then treatment lasting many sessions may be required. First the dysfunctional thinking will need modifying, next relaxation training and coping strategies may be required for the emotional components, and finally, problem solving approaches may be advocated in order to substitute more appropriate and constructive thinking. Such approaches have shown some promise in a number of difficult areas, such as child abuse.[6]

When significant child behaviour problems, parent dysfunctional thinking, and emotional problems coexist, then it is likely that family rules governing child behaviour may become loose and inconsistently applied. It is of course difficult to track behaviour when the general rules are unclear. As already hinted, it is therefore important in early therapy to spend time discussing rules For instance, what are the absolute 'don'ts' (for example, no throwing things around, no verbal abuse to parents, etc), what behaviour is expected at mealtimes, homework times, and so on.

One very important area of parent thinking centres on expectations about child behaviour. Are the expectations of the child, given his or her particular developmental level, appropriate? The child abuse literature frequently refers to the inappropriate expectations that such parents have of their children.[7] For instance, they may expect the child to exhibit high levels of self control at very young ages, or they might expect their baby to respond exclusively to them without being able to appreciate the need for interactional sensitivity and flexibility. Some years ago the author treated an 18 month old child who presented with a six month history of persistent crying. Being behaviourally orientated, an interactional understanding of the problem was sought in terms of attention versus non-attention. Within this framework the results of a prolonged observation failed to produce answers. However, when concepts such as maternal sensitivity to the child were considered, the nature of the problem became clear. Observation showed that the mother was attending to the child indiscriminantly in the sense that she failed to respond to social cues emitted by the child. Some simple parent coaching on such issues produced a dramatic resolution within 24 hours! Thus behavioural assessments in general are incomplete unless the parents' complaints of the child behaviour are seen within the context of normal child development. In some cases then, it may be the parents' expectations which require modification and not the child's behaviour.

An early exploration of parent expectations about treatment and about the future is also often useful. Understanding what they expect from the treatment may reveal useful information about motivation. Generally parents pushed into therapy by outside agencies may view such negatively and as unhelpful. If this can be addressed early on, then it may be possible to bring about a more positive attitude to therapy. An exploration of the future may be beneficial in two ways Firstly looking at what may happen if the problems persist may help generate further motivation to attempt change now. Secondly looking at the future ramifications of positive change for the child and parent may not only help motivation, but may also suggest future actions that might solidify change. For instance, given positive changes, what will you and your child be able to do in the future that you can't do now?

THE PROBLEM BEHAVIOUR

Ask a number of people to define what they mean by child tantrums, and you will find that the definitions vary considerably from person to person. Such a simple test clearly illustrates the importance of gathering very specific information about the occurrence of the problem behaviour, its frequency, and where it occurs. This becomes even more important when parental complaints are vague. For instance, with complaints such as, 'she is anxious', one would want clear episodic data about what she does, says, and what emotions are expressed. Information of this type may reveal that the parents' concerns about the problem are justified, or that their perception of the behaviour is in some way erroneous. For instance, depressed parents often perceive child behaviour as more problematic than it is,[8] or multidistressed parents may exhibit inappropriately high standards when making judgments about child behaviour.[7] Clearly, such findings have ramifications for the treatment focus. In other instances information may reveal that the parents have not actually observed the problem of interest and typical examples of this include intersibling fighting as already discussed. Finally, accurate descriptions of the behaviour will, where appropriate, facilitate the therapist in making judgments about what opposite prosocial behaviour might later be reinforced.

BEHAVIOURAL CONSEQUENCES

Knowledge of the consequences of problem behaviour will obviously increase our understanding about why the problems persist. Interest in consequences will, in most instances, focus upon exactly what they are, how frequently they occur, how appropriate they are, and how consistently they are applied. Spreading the inquiry into common positive and negative consequences employed by the parent will also hint at what ones may, with or without modification, be utilised later. Finally, information on the relative density of negative or positive ones will be important as this too may require later therapeutic consideration. To illustrate: research in families with aggressive children has shown that often parents use a preponderance of negative to positive consequences.[2]

Previous reference was made to the parent belief that nothing works. In such cases, careful inquiry into what rewards and punishments they consider don't work may actually reveal that these techniques (as the parents see them) have paradoxical effects. In other words, when the smack is applied the child behaviour worsens, or when the parent praises, the appropriate behaviour decreases. Clearly, in these cases the techniques are not being employed at sufficient intensity or their timing is inappropriate. In treatment, appropriate corrections or other consequences will need to be found.

There is a frequent tendency in therapists to consider immediate consequences and to ignore ones occurring more distantly. For example, when a mother gives in to a child's refusal to go to school, the child ceases his distress and the mother's giving in is reinforced. However, later we may find the child watching television and enjoying his mother's company. Here the child receives further and later reinforcement (sometimes referred to as secondary gain) for his refusal behaviour. Such important consequential arrangements require attention and can only be addressed if we proceed in our exploration of the problems with questions such as, 'and then what happened next'.

Assessment methods

Parent trainers have employed a range of assessment techniques and these have included interviews, direct observation, various questionnaires, and parent records. Here the focus of attention is on interviews and parent records.

A perusal of many texts on parent training written over five to 10 years ago reveals an overwhelming preoccupation with observational methods of assessment. No doubt this resulted considerably from an interest in achieving objectivity. Also, much of the parent training development occurred within research settings, where the luxury of careful and painstaking observation of interaction was feasible. Clinicians in the service sector are frequently unable to spare such time, and therefore, must rely on methods that are less time consuming. Fortunately, in recent years, parent trainers have for a number of reasons shown an increased interest in interviewing.[9] Firstly the recognition that events not readily observable, such as parental disputes and what they thought, are important has resulted in more attention. Secondly, the realisation that success is not only about observable changes, but also about changes in beliefs and attitudes (which are less immediately observable) has been influential in shaping assessment methods.

Research into interviewing methods has clearly demonstrated that it is possible to obtain high quality factual information about family life, without necessarily hindering the important development of the therapist/client relationship (see later).[10] This author would go further and state (on the basis of teaching experience), that many therapists do not realise that interviewers can gain clear interactional information. Practically speaking, a careful inquiry into recent behavioural episodes, sequence by sequence, can be achieved if the interviewer adopts an attitude that he would like to be able to visualise the episode in the manner of a video recording. Obviously, while such interviewing skills can never completely override the potential value of observing events, for the service clinician they can function satisfactorily as a major assessment method.

Parent observational records of behavioural episodes serve several purposes. Further information about the problem is gained, the parents' attention is focused more specifically on the problems, and finally in consequence they can begin to observe more accurately as was mentioned earlier. Unfortunately, clinical experience indicates that parents are poor at keeping detailed records—and this is despite careful instruction and training. On visits to the clinic it is often readily apparent that their records lack detail or were completed shortly before the appointment. One can improve this by telephone checks between appointments, or by asking for audio recordings of episodes made at home, and finally the therapist can use the scanty records as a starting point for further focused interviewing as already discussed.

Some thoughts on treatment

Careful assessment will in most instances suggest the most appropriate treatment techniques. Such will include ensuring that the situations are maximally conducive to behaviour change through encouraging clear rules, ensuring time is available to manage the problems, optimising the parents' general approach, and coaching in the use of a variety of techniques such as positive reinforcement, differential attention, time out, and point or star systems. Some discussion has already taken place with regard to things that might be changed in order to increase the probability of appropriate behaviour. The specific techniques of change are not discussed here. Rather, in this section some general and important issues relating to their application are examined.

THERAPIST SKILLS

A number of research reports over the past 15 years have drawn attention to the importance of therapist skills in bringing about positive change. For instance, Alexander *et al*, in working with delinquent families, demonstrated that a therapist's ability not only to empathise accurately, but also to direct families clearly, contributed significantly to the likelihood of successful outcome.[11] Wahler and Dumas, in treating multiproblem families, have drawn attention to the importance of adopting a friendly, non-coercive style.[5] Finally, Patterson and colleagues (cited in Twardosz and Nordquist) have begun to examine therapist skills mainly as a consequence of inconsistent results in some of their parent training programmes.[12] Obviously the requisite therapist skills will vary from case to case. In those where problems are mild and parents highly motivated, straightforward direct quickly given advice may be sufficient. However, in more difficult cases, the therapist will often need to create an atmosphere in which the client feels acknowledged, supported, and encouraged to consider the resolution of their problems in a positive light. Early directing and teaching may simply drive some of these parents away. In the end, failure to give credence to the importance of therapist skills will result in resistance in therapy and possible subsequent treatment failure.

LEARNING THERAPY TECHNIQUES

Popular books such as *Toddler Taming* contain much sound practical advice that could benefit many of the parents seen at busy outpatient clinics.[13] However, and unfortunately, many seem unable to transfer the information into action. Clearly, the distance between the written word and successful application is vast, and also such material frequently fails to address the individualistic nature of parent-child difficulties.

How then can parents best learn to effectively apply behavioural techniques?

A number of studies have demonstrated that parents learn most effectively when techniques are role played or rehearsed and least well when the knowledge is imparted didactically.[14] The former teaching methods are time consuming, and thus in busy clinical practice one has to find some kind of reasonable balance. One possible solution is to train small groups of six to seven parents. This has been done and would appear superficially to address the time problem.[15] Additionally, working with parents in groups can in itself be facilitative, because it offers a forum in which parents can discuss and communicate their problems and solutions. Unfortunately, arranging convening and administering group sessions can be costly in terms of time, and this is something that is often inadequately addressed in the literature. Another approach is to employ prepared film and video demonstrations.[12] Though this has received some attention, this author would suggest that it has not been explored in this country to its full potential. Overall, one could argue that further research is required into each of these different training methods. However, the reality probably is that the different training methods are each in their own ways effective, but that their use needs to be matched carefully to the varying needs of different clinical samples.

ANTICIPATING ROADBLOCKS IN TREATMENT

As has been indicated, careful assessment should hint that at the optimal treatment approach and thus help reduce problems that might occur in therapy. However, there are a number of commonly recurring themes within treatment which are worth addressing.

Many parents do not readily appreciate that behavioural change in themselves and child is time consuming, and that in consequence (as is the case with learning any new skill) space and time requires to be created. For instance, in attempting to help a child develop homework skills, it is advisable as far as is possible to ensure that other household tasks occurring at the specified time take a secondary role. In all behavioural management applications it is important to discuss this with the parents with a view to encouraging maximum effort and, in consequence, reduce the negative influence of other competing events.

Secondly, standard techniques and approaches will never suit all parents. For instance, some parents might prefer to use a bedroom for time out and others prefer a kitchen corner. Similarly, when managing disruptive mealtime behaviour, some parents may have no difficulty in removing food until the next mealtime, but others may be unwilling to go this far. In all cases, therefore the treatment techniques require to be presented, discussed, and then tailored to suit individual needs. Throughout such discourse one of the therapist's functions will be to ensure that what is being applied fulfills the therapeutic requirements, for example, that the positive reinforcement really is reinforcing to the child

Thirdly, parents require to be made aware that the behavioural problems may, in early treatment, increase and intensify before they improve. This is important as some parents may read the worsening as a sign, that the techniques are not working, or worse still are damaging their child. Once this point is understood then parents may hopefully read the worsening signs with encouragement and thus muster further effort.

Fourthly, experience teaches us of some of the manipulative craft which children can exhibit during behavioural programmes. For instance, the child may adopt an, 'I don't care attitude', or may elicit parental guilt through statements such as, 'you don't love me', 'you're cruel to me', etc. Viewed from a distance, the manipulative repertoires of some children can be both creative and amusing. Parents often require to be warned.

Finally, throughout treatment therapists require continually to hold the question, 'I wonder what might prevent successful application', at the back of their minds. For example, how do we manage interfering adults, the presence of siblings, and the fact that parental tiredness may create difficulties in managing problems in the middle of the night.

COURSE OF TREATMENT

If one is to modify successfully parent-child behaviour, then contact requires to be quite frequent. There is little use in initially seeing parents and children on a monthly basis. Not only do parents require frequent encouragement and support, but also they require help with early teething problems, and some of these have been referred to in the sections immediately above. At first sight, this may appear time consuming, however much of this early work can be conducted by telephone. In fact, in many milder cases treatment may work very well with one or two clinic visits and the remainder of contact made by telephone. Once treatment has begun to succeed, then follow up at less frequent intervals is advisable for up to one year, as research findings have demonstrated that many families require booster treatment throughout this period.[2]

EFFECTIVENESS OF TREATMENT

Both clinical experience and research have shown that training parents to manage their children's behavioural problems is effective. The treatment approach would appear to work best when problems are mild, are of the acting out type, are of short duration, and where the general family background is shown to be relatively stable. Conversely, when problems are extensive, have been present for years, and occur in a context of multiple other problems, then treatments show little in the way of durable effects.[16] Of those cases that fall between these two extremes, the question of success is much more difficult to answer.

The issue of determining success rates is further compounded by a host of variables that include the specific types of problems, the duration and intensity of the therapy, the quality of therapy (for example, were the therapists experienced or just newly trained), and finally what it is that actually constituted success. With regard to the latter point a number of issues arise. Many single case studies and reports concentrate on reductions in difficult behaviour, and neglect whether or not the child shows significant increases in prosocial skills, generalisations of changes across environments and relationships, and changes in internal states such as might be reflected in measures of self esteem. Equally, success must be allied to how parents think, perceive, and view the situation as in the first instance they have often been responsible for the referral.

Perhaps it is unrealistic to expect much more at this time. After all the social learning theories underpinning parent training are still largely hypothetical, and secondly, our knowledge of how family events such as marital problems effect and interact with the individual child over time is still largely in its infancy. Finally, there is a feeling that much of the literature's use of the word success is synonymous with cure. Kendall quite rightly asserts that the notion that people can be 'fixed' is unreasonable and unhelpful.[17] For instance, if our successfully treated school refuser returns with further problems three years later, this is not necessarily indicative of past failure, but rather indicates that more therapy is required. The conclusion we can draw is that if we can be helpful at one moment in time then our function becomes more realistic, credible, and healthy.

Concluding remarks

This brief examination of parent training in behavioural child management has focused only on some aspects considered important by a practising clinician. Many areas have not even been considered. These, among others, include observational methodology, common treatment techniques such as time out and differential attention, contingency contracting procedures, coping and problem solving strategies, and a range of adjunctive treatment procedures designed to improve and enhance outcome. For further information the reader is referred to a number of useful source books listed in the appendix.

The majority of developments in parent training have taken place in research settings, and while such development continues there is an urgent need to conduct efficacy studies in the routine clinical sector in order to establish how the technology will stand up when time is short and caseloads are large. Hopefully, the new emphasis on medical and clinical audit will serve as well in this direction over the next decade and beyond.

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6 Wolfe DA Child abuse In· Hersen M, Hasselt VB, eds *Behavior therapy with children and adolescents*. New York. Wiley, 1987 385–415

7 Wolfe DA *Child abuse* London. Sage, 1987.

8 Webster-Stratton C, Hammond M. Maternal depression and its relationship to life stress, perceptions and child behavior problems, parenting behaviors, and child conduct problems *J Abnorm Child Psychol* 1988;**16**:299–315

9 Mash EJ, Terdal LG Behavioral assessment of child and family disturbance In Mash EJ, Terdal LG, eds *Behaviour assessment of childhood disorders* New York Guilford, 1988 3–65

10 Cox A, Rutter M Diagnostic appraisal and interviewing In: Rutter M, Hersov L, eds. *Child and adolescent psychiatry: modern approaches* Oxford. Blackwell, 1985 233–48

11 Alexander JF, Barton C, Schiavo RS, Parsons BV Systems behavioral intervention with families of delinquents therapist characteristics, family behavior and outcome *J Consult Clin Psychol* 1976;**44**:656–64

12 Twardosz S, Nordquist VM Parent training. In· Hersen M, Van Hasselt VB, eds. *Behavior therapy with children and adolescents* New York John Wiley, 1987

13 Green C. *Toddler taming* London· Doubleday, 1990

14 O'Dell SL, O'Quin JA, Alford BA, O'Briant AL, Bradlyn AS, Giebenhain JC. Predicting the acquisition of parenting skills via four training methods *Behavior Therapy* 1982, **13**:194–208

15 O'Dell SL Progress in parent training In. Hersen M, Eisler RM, Miller PM, eds *Progress behavior modification* New York Academic Press, 1985: 57–108

16 Wahler RG, Graves MG Setting events in social networks ally or enemy in child behavior therapy. *Behavior Therapy* 1983,**14**:19–36

17 Kendall PC The generalization and maintenance of behavior change: comments, considerations, and the 'no-cure' criticism *Behavior Therapy* 1989,**20**:357–64.

Appendix

The child behaviour therapy books listed are ones that the author has found most useful. This list is by no means exhaustive, but should provide readers with a fairly broad coverage of the field of child behaviour therapy.

CHILD BEHAVIOUR ASSESSMENT

The one text listed here, which is now in its second edition, is authoratative and has become a standard bench book. In addition to chapters on conduct, emotional and developmental problems, there are also ones on brain injury, chronic pain, obesity, anorexia nervosa, eneuresis, encopresis, child abuse, and others. The breadth of coverage has hitherto been unusual in behaviourally oriented textbooks.

1 Mash EJ, Terdal LG, eds *Behavioral assessment of childhood disorders* New York: Guilford, 1988.

THERAPIST HANDBOOKS

The two books here provide therapists with detailed guidelines for conducting child behaviour therapy assessment, treatment planning, treatment implementation, and outcome evaluation. Both texts are practical and contain a wealth of clinical experience.

1 Herbert M *Behavioural treatment of problem children* London: Academic Press, 1981.

2 Herbert M. *Working with children and their families* London. Routledge, 1988.

CHILD BEHAVIOUR THERAPY HANDBOOKS

The two books listed deal with a wide range of different childhood disorders and problems. The author prefers the second text, mainly because of its masterly coverage of vast areas of behaviour therapy literature. Unfortunately this text is now rapidly becoming rather dated.

1 Hersen M, Van Hasselt VB, eds *Behavior therapy with children and adolescents* New York Wiley, 1987
2 Ross AO *Child behavior therapy principles, procedures and empirical basis* New York. Wiley, 1981

CHILD BEHAVIOURAL MANAGEMENT MANUALS

The three books listed provide basic information on the management of a range of child behavioural problems. Generally they are fairly straightforward and not too laden with technical jargon. The author prefers the first book, as not only does it contain much about practical management advice, but also it addresses many of the practical problems encountered in counselling parents.

1 Barkely RA. *Defiant children* New York Guilford, 1990.
2 Green C *Toddler taming*. London. Doubleday, 1990
3 Patterson GR. *Families* Champaign, Illinois: Research Press, 1977.

Archives of Disease in Childhood 1992; 67: 543–549

PRACTICE ABROAD

Paediatric illness in Hong Kong and Britain

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The territory of Hong Kong (area 1071 sq km), is made up of Hong Kong island, the Kowloon peninsula and the New Territories, the latter comprising mainland and over two hundred islands. Huge urban conurbations (many built on new land claimed from the sea and previous agricultural areas) have sprung up as pressures have grown to accommodate an ever burgeoning population that has expanded from 0·5 million in 1945 to nearly six million in 1990. Enormous social and economic changes have also taken place as Hong Kong has emerged as one of Asia's most rapidly developing newly industrialised regions. A total of 98% of its people are Chinese, mostly from the southern provinces of China.

Improvements in childhood mortality are a revealing marker of these changes. In 1956 infant mortality was 60·9/1000 and in 1989 it was 6·9/1000.[1] Perinatal and neonatal mortalities in 1989 were 7·6/1000 and 4·8/1000 respectively and for children under 5 years was 8·2/1000.[1] These impressive improvements have been achieved despite periodic influxes of huge numbers of people from mainland China caused by various social upheavals in that country, migrations that would have dealt a crippling blow to the health and social services of most nations. The sorry plight of children in Hong Kong as little as a generation ago was vividly described by Professor Elaine Field and Dr Flora Baber in their classic monograph *Growing up in Hong Kong* where they describe the appalling living conditions of thousands of children in the 1960s, their often meagre nutritional state, and their affliction by widespread scourges of infections and infectious diseases.[2] But how times have changed. Living conditions, through remarkable economic achievements, have improved beyond recognition. An outstanding Maternal and Child Health Service has (though still too often unappreciated) contributed so much to improve the physical well being of mothers during pregnancy, the safety of childbirth and the health of children through immunisation, physical and developmental surveillance, and general primary health care. The secular increase in physical size of Hong Kong children over the past 20 or so years of record keeping is further testament to these improvements.[3 4] Hospital facilities for sick children, including services for the newborn, have also greatly improved and there has emerged a progressively higher overall standard of paediatric care both inside and outside hospital, helped significantly by expansions in postgraduate education and professional training programmes.

In 1982 I arrived to spend what was to be seven years in Hong Kong. I had presumed that in a part of the world where the ravages of poverty, malnutrition, and infectious diseases belonged largely to the past, the clinical problems in children would be not that dissimilar from those in Britain, except for some obvious genetic disorders. But in quite a short time I was to discover many intriguing and unexpected variations in morbidity that reflected genetic influences and the impact of lifestyle and socioeconomic conditions on the growing child. Returned now to paediatric practice in Britain these variations in morbidity have become especially vivid. In this paper I have chosen to reflect on those conditions with particularly striking variations or that hold a certain personal intrigue for me.

Genetic disorders

The genetic disorder mostly frequently found in Hong Kong is *glucose-6-phosphate dehydrogenase (G6PD) deficiency:* 4·4% of males and 0·4% of females have been estimated to be affected.[5] Not so long ago this disorder was a dreadful scourge that made a big contribution to death in the newborn period and, in the long term, to severe neurodevelopmental disability from kernicterus. In 1971 cord blood screening was introduced into a couple of hospitals and then in 1984 G6PD screening, using a quantitative assay of the enzyme activity on cord blood, was introduced throughout the territory under the direction of the Clinical Genetic Service of the then Medical and Health Department. Now, mothers and fathers of all diagnosed babies are counselled and given written information to help them understand the disorder. Admission of children to paediatric wards with haemolytic crises is now a rarity.

Thalassaemic syndromes are the most common autosomal recessive conditions among the southern Chinese. *α-Thalassaemia* is still an importance cause of stillbirth and each year approximately 25 infants are born with *β-thalassaemia major.* The *β-thalassaemia trait,* prevalence about 2·5%, accounts for many children having an incidental finding of a haemoglobin concentration below 110 g/l, but is rarely symptomatic and does not require treatment.[6]

Of genetic disorders not seen in Hong Kong compared with Britain *phenylketonuria* and *cystic fibrosis* are those most conspicuously absent. The story of phenylketonuria is especially intriguing. A study in the early 1970s of about 18 000 newborn babies screened in the new born period did not turn up any cases of phenylketonuria (Dr Henrietta Ip, unpublished data), seeming to confirm local paediatric claims that phenylketonuria is not found in Hong Kong. A contrary opinion, however, emanates from parts of mainland China, especially Shanghai, Beijing, and Guangzhou, where phenylketonuria has apparently been diagnosed leading to neonatal screening programmes being introduced. One study from the First Affiliated Hospital of Beijing Medical University of 198 230 newborns screened by Guthrie's bacterial inhibition assay described an overall incidence of 1/16 500, rates similar to those found in white populations.[7] I did, however, meet some scepticism over these findings in Hong Kong where phenylketonuria is not included in the neonatal screening programme, newborn screening being confined to G6PD deficiency and congenital hypothyroidism (with an incidence similar to that reported in white and other Asiatic populations of about one in 3500).[8] I did not come across any child in the many schools and institutions for the mentally handicapped whom I could recall with hair fairer than usual and anything other than dark brown eyes, claims that have been made in some parts of China to support the occurrence of phenylketonuria.

It is intriguing how cystic fibrosis appears also not to have been described in the Chinese as it has been reported in Japan.[9] With the recent cloning and sequencing of the gene responsible for cystic fibrosis the reason for the absence of this disease might soon be explained. Could it be that there is an abnormal mutation of the gene in the Chinese but not the one that results in the characteristic phenotype?

Conditions determined before birth

Preaxial polydactyly is much more common in Hong Kong.[10] The spectrum of congenital heart disease is also slightly different with *univentricular heart* and *severe right ventricular outflow obstruction* in the newborn more common and *left heart abnormalities—aortic stenosis, hypoplastic left heart, aortic coarctation*—less common than in white populations.[11] [12] Remarkable in its virtual absence is *spina bifida* (anencephaly does occur but usually as part of syndromes of multiple congenital anomalies). A study from Tsan Yuk Hospital (University of Hong Kong) of the incidence of neural tube defects among all deliveries in 1961–80 (123 491 births) showed incidences of anencephaly, spina bifida, and encephalocele of 0·83, 0·12, and 0·06 per 1000 births respectively.[13] Comparable incidences of spina bifida in the UK were then 1·5–4·1/1000. Between 1984 and 1990 in the Prince of Wales Hospital[*] (about 30 000 births) there were 15 cases of anencephaly, two of encephalocele, three of meningomyelocele (all in south Asian babies), and two of meningocele (Dr T F Fok, personal communication). The southern Chinese diet typically is rich in green vegetables, fresh fruit and rice, thereby providing a substantial amount of folic acid. Methods of cooking vegetables (rapid stir frying or by brief steaming) would be expected to preserve folic acid content better than western cooking practices where vegetables are often overcooked in boiling water. Apparently in north China spina bifida is as common as it used to be in many western countries (Professor Michael Laurence, personal communication). In these regions diet is influenced by season and fresh vegetables are scarce for much of the year. Some Chinese medical opinion has linked this higher incidence of spina bifida with a much lower folic acid intake (H Ye, Symposium on Paediatrics in China and Africa, Royal Society of Medicine, London 1986). All this does more than provide a hint that the southern Chinese could be protected by their diet from abnormal neural tube embryogenesis, supporting the currently held view that folic acid sufficiency is needed to prevent the expression of genetic predisposition to neural tube defects.

Later gestation gave the impression of providing further protection for the fetus. Intrauterine growth retardation is much less common, the thin scraggy, 'small for dates' baby being an unusual sight. The ratio of mid-arm circumference to occipitofrontal circumference, an index of late gestation growth retardation, is significantly higher than in Asian, white, and black neonates in London.[14] There is also a lower incidence of very low birth weight in Hong Kong: Lau and his colleagues in 1984 described an incidence of infants weighing <1500 g at birth of 6·9/1000,[15] considerably lower than the 14·4/1000 described over the same period in England and Wales. But such low incidences are not peculiar to Hong Kong Chinese, being reported also in Shanghai,[16] and in Chinese populations in Australia.[17]

I suggest these more favourable intrauterine conditions are related to social factors and less maternal hypertensive disease. Teenage pregnancies are still uncommon and smoking and alcohol consumption during pregnancy very unusual. Diet in pregnancy is excellent and antenatal care in the maternal and child health clinics and hospital is very strictly supervised and full advantage is taken by most pregnant mothers. Hypertension in pregnancy is also less common in the Chinese.[17] [18] Since the early 1960s when mortality data began officially to be gathered, perinatal and neontal mortalities in Hong Kong have been consistently lower than in Britain. In 1965, a time when environmental conditions in Hong Kong were extremely harsh for so many of its people, perinatal mortality was 23/1000 compared with about 31/1000 in Britain,[19] further supporting my contention that some inherent protection is conferred upon the Chinese baby before birth.

Problems in the newborn

There is a very low incidence of *congenital dislocation of the hip*, at least 10 times less common than in white babies.[20] One explanation from recent ultrasound studies is that acetabular morphology of the hip joint in Chinese babies might be more favourable, causing less potential instability.[21] The most common clinical problem in the newborn is *neonatal jaundice*. Babies in Hong Kong are born in hospital or in one of 47 maternal and child health centres scattered throughout the territory. Altogether 50–70% of normal term infants in Hong Kong have a serum bilirubin concentration >171 mmol/l.[22] Reasons for such a high incidence of jaundice, that I used to consider of the 'exaggerated' physiological type, an imbalance between production and excretion of bilirubin, is unknown. In 1984 a study from Singapore where jaundice among Chinese babies is also very common, showed a significant association between raised cord blood α fetoprotein and subsequent jaundice in full term normal babies, inferring an immaturity of hepatic enzyme conjugating mechanisms.[23] A study in Hong Kong in 1984 suggested that a slightly increased rate of haemolysis, as measured by carbon monoxide excretion, could be contributory.[24] Another view has been that jaundice could be associated with mothers consuming certain herbal medicines during pregnancy, a tradition still popular in Hong Kong where many of these herbs are held to have beneficial effects on the process of childbirth.[22] In times past newborn babies were also often given herbs by their mothers to help rid them of 'placental toxins': this practice, though much less common, still prevails, especially in the older parts of Hong Kong. In vitro studies have shown that a very popular herb, chuen-lin, can displace bilirubin from its albumin binding sites,[22] but which of the 30 or so ingredients is the active principle is not known. In a 1985 study from Tsan Yuk Hospital, 54% of about 10 600 mothers admitted to multiple herb consumption during pregnancy.[25] But contrary to other reports, and further complicating the issue, there was no significant association between maternal herb consumption during pregnancy and the extent of neonatal hyperbilirubinaemia: neither were G6PD deficient babies more severely jaundiced as a consequence of herb consumption by the mother. The intriguing association between herbs and neonatal jaundice has yet to be resolved.

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[*] Frequent reference is made in this article to paediatric experiences in the Prince of Wales Hospital from the time of its opening in 1984 to when I left Hong Kong in 1989. This large, regional government hospital of 1428 beds is in Shatin, a huge new urban area in the New Territories and linked to north Kowloon by road and rail. The hospital accommodates the new clinical faculty of medicine of the Chinese University of Hong Kong. Its department of paediatrics with 218 medical beds (including neonatal cots) offers inpatient and outpatient services for a population now of about 1·5 million people, about 25% under 16 years of age.

But no longer is jaundice the devastating scourge it used to be. In 1971 in the University Paediatric Unit, Queen Mary Hospital, 8·7% of term infants who developed neonatal jaundice developed kernicterus.[26] Phototherapy, introduced about 20 years ago, has radically changed the face of jaundice with exchange transfusions now rarely needed. It is held also that somehow socioeconomic improvement has contributed significantly to this dramatic decline in severe jaundice (Professor C Y Yeung, personal communication). Neonatal jaundice persists not as a worrying medical problem but more of a social irritation causing separation of baby from mother in the early weeks after delivery with all its inconveniences, high bed occupancy in the neonatal nurseries, and a huge primary care burden for doctors and nurses working in the territory's many maternal and child health clinics.[27]

I cannot leave the newborn period without mentioning the tremendous achievement in the 1980s of the interruption of perinatal transmission of the hepatitis B virus (HBV) at birth by early vaccination and passive immunisation. There is an appalling toll in South East Asia from the HBV carrier state with hepatocellular carcinoma, hepatic cirrhosis, and carcinoma of the stomach, which are the causes of so much premature death in middle life. Many countries in Asia have now confirmed the perinatal period as the most important time for transmitting HBV, resulting in carrier status. In Hong Kong all pregnant women are checked for HBV antigen status during antenatal visits. Babies of carrier mothers are given hepatitis B immunoglobulin together with a first dose of vaccine at birth followed by two further doses of vaccine at 1 and 4 months (a routine now also given to all babies of non-carrier mothers). Almost at a stroke the devastation caused by the carrier state one generation from now will have been virtually eliminated.

Problems in infancy and childhood

With childhood mortality rates in the 1980s ranked alongside the best in western countries it was a surprise to me to discover when first I arrived in Hong Kong that substantial local opinion held that undernutrition, especially of energy, calcium, vitamin D, and iron, was a continuing problem.[28] My immediate impression was that the children looked a little smaller than those in Britain but they did not give any impression of being undernourished. A five year longitudinal study in our department of growth and nutrition in babies born in the urban area of Shatin showed that between 6 and 18 months there were certainly downward deviations in weight gain, and height and head circumference growth viewed against the National Center for Health Statistics (NCHS) reference curves.[29 30] Skinfold thickness growth also showed much less adiposity than in white infants.[31] Yet intakes of major nutrients were all well within recommended dietary recommendations.[29 32 33] One fascinating feeding practice was the regular use by mothers of compound herb preparations when reconstituting milk formula,[34] a practice believed to stimulate the baby's appetite, enhance absorption of nutrients from the gastrointestinal tract, and help eliminate excess endogenous heat.

These very distinctive growth profiles in well nourished children, and which are also found in children in many other healthy Asiatic populations,[35] made us question the advisability of using the NCHS curves as a suitable reference for the southern Chinese. We were concerned that reluctance to recognise adequate nutritional status could lead all too easily to overfeeding and a shift away from the excellent Cantonese diet, nutritionally so well balanced with its low intake of saturated fat (30% of the total energy content[36] compared with approximately 50% in the diet of British children[37]) and refined carbohydrates and high fibre and protein. But remarkably few were breast fed. Of about 25% put to the breast at birth in our study only 8, 6, and 2% were still breast feeding at 2, 4, and 6 months respectively.[30] Very low rates of breast feeding are widespread throughout Hong Kong. This is due chiefly to misconceptions held by mothers over the value of breast feeding, the ready availability of approved milk formula, the need and desire to return to work soon after delivery, short maternity leave, lack of privacy, and an urgent life style. This is also the case in other newly industrialised countries of South East Asia. The economically rich Orient is neglecting breast feeding, but to what future cost?

Gastroenteritis, due chiefly to rotavirus, was common, accounting for about 14% of all paediatric admissions to the Prince of Wales Hospital in the mid 1980s.[38] But most of these children were admitted for medically trivial reasons: gastroenteritis is no longer a serious medical problem in Hong Kong. Rarely were babies seriously dehydrated on admission to hospital. Because of a higher incidence of genetically determined deficiency of lactase in the Chinese secondary lactose intolerance might be expected frequently to complicate gastroenteritis: surprisingly it was rare, no more common than in this country. Far more frequent were iatrogenic complications of the treatment of gastroenteritis by outside practitioners: paralytic ileus and electrolyte disturbances from treatment with antimotility drugs were not infrequently found in children admitted to hospital. *Pyloric stenosis* was very uncommon. During the 1970s and 1980s the incidence in Britain was approximately 5/1000.[39] In 1986–91 there were only 14 cases seen at the Prince of Wales Hospital (approximately 0·27/1000; Dr K Liu, personal communication). *Coeliac disease* does not occur in the southern Chinese (although I have been told of some evidence from north China, where wheat is consumed more than in the predominantly rice consuming south, that this disorder is known there). *Failure to thrive* was not a common hospital problem: adverse social factors at home and poor parenting skills were not the associated risk factors they are so often found to be here, an example of the protection afforded to the young infant by support within the family that is still a strong feature of Hong Kong life despite its high degree of urbanisation. In older children the chronic bowel inflammatory diseases, *ulcerative colitis* and *Crohn's disease,* are non-existent, as indeed they are in adults. Hong Kong is far from a Garden of Eden for the paediatric gastroenterologist!

I was very surprised when I went to Hong Kong to discover how little aware were paediatricians there about *cot death* (SIDS).[40] But Hong Kong was not alone in being so unaware of cot death. Paediatricians in China and other South East Asian countries confirmed a similar very low incidence. (In America the incidence of cot death has also been reported as lowest in the Asians.[41]) In a prospective study between 1 December 1986 and 31 November 1987, covering 70 519 births, only 21 cases of cot death were recorded in the whole of Hong Kong, an incidence of 0·29/1000.[42] Comparable incidences in Britain were then about 2–4/1000. To explain this much lower incidence we wondered whether the 'microenvironment' of Hong Kong infants with crowded living conditions leading to babies never being left alone (a marked contrast to the solitary sleeping habits of so many western babies) might somehow protect, perhaps through an influence on the control of breathing at a particularly vulnerable developmental stage. We wondered also, as have many others since, whether supine sleeping might also protect as traditionally Chinese babies in Hong Kong are seldom put to lie in the prone position for fear of suffocation; 44% of the index babies in our study compared with 7% of controls had this sleeping posture.[42] Supine lying does not increase risks of choking as is still widely taught in Britain. I believe that protective influences exist for cot death that are linked with cultural attitudes to infant care. There is somewhere an 'ethnic–geographical' clue to help us better understand the aetiology of SIDS and it is now well overdue that we look at cot death in a more anthropological perspective.

Iron deficiency still arouses concern in Britain with reported prevalences at 12–45% in major urban areas[43] and especially common in non-white children. Held responsible are poor weaning diets and widespread consumption of pasteurised cows' milk with its negligible amount of iron and risks of causing gastrointestinal blood loss.[44] In Hong Kong, and despite concern in the recent past about dietary deficiencies of iron, calcium, and vitamin D during weaning, we were able to show virtually no iron deficiency (<2%) at 18 months when weaning had been largely completed.[32] There was also no nutritional vitamin D deficiency[33] other than in some Vietnamese children and those more recently arrived from mainland China. With maternal and child health clinics recommending affordable iron and vitamin fortified formulas as breast milk substitutes well into the second year along with an excellent weaning diet and exposure to plenty of sunshine, it is not surprising that what are among the most common nutritional deficiencies in so many other parts of the world, developed and developing alike, are so infrequent in Hong Kong.

Kawasaki disease is far more common than in Britain,[45] although nowhere near the high incidence of Japan. Fifty five children were diagnosed at the Prince of Wales Hospital in 1987–90 (Dr D Leung, personal communication). I was surprised to find *Myasthenia gravis* in young children occurring more frequently than in white children. In its early onset, mild natural course, and frequent spontaneous remissions[46] it is limited mostly to fatiguability of the ocular muscles: children usually present with ptosis and ophthalmoplegia and sometimes as young as 2 years of age. There is a strong association with the histocompatibility complex HLA-DRw9, a genetically determined variant occurring more often in Chinese.[47] Children presenting with extrapyramidal dyskinetic symptoms, *oculogyric crises,* caused by drugs often prescribed by general practitioners such as prochlorperazine (prescribed for upper respiratory symptoms) and metoclopramide (for vomiting) and complication of some Chinese medicinal treatments were commonly seen.[48] Their prompt recognition in accident and emergency departments as a cause of bizarre acute neurological symptoms was important as intravenous diphenhydramine would rapidly reverse the symptoms.

Acute poststreptococcal glomerulonephritis is still far more common than in Britain, though rheumatic fever, the other important streptococcal related illness, is exceedingly rare. Over five years, 1984–9, only two children were diagnosed in the Prince of Wales Hospital to have rheumatic fever in contrast to 216 with acute nephritis. Of 74 children with acute nephritis admitted over an 18 month period in 1984–6 preceding streptococcal infection was as much in the skin as in the throat.[49] Barely a month would go by without a child being admitted with serious *upper gastrointestinal bleeding*. One study from the Division of Paediatric Surgery, Queen Mary Hospital, recorded as many as 49 children admitted with upper gastrointestinal haemorrhage between 1985 and 1988.[50] This bleeding in young children was usually attributable to multiple superficial gastric erosions and there was more than a high index of suspicion to blame aspirin and steroids contained in some medications prescribed outside hospital. *Systemic lupus erythematosus* is well recognised to occur more often in Chinese people[51] and this was evident in Hong Kong hospital paediatric practice, girls particularly being affected. A serious multiple system disease, systemic lupus erythematosus is a common cause of end stage renal failure in Hong Kong. In contrast *insulin dependent diabetes mellitus* was much less common.

Child abuse and the enormous range of problems encapsulated by this diagnosis provided appreciable contrasts. The first case of child abuse in Hong Kong was officially documented in 1979 and since then its manifold physical and emotional components have increasingly become a major focus of medical and social concern. There is no systematic documentation of its incidence but there is no doubt that non-accidental physical injuries, for example bruises, burns, bites, lacerations, fractures, subdural haematoma, etc, which are problems that have been increasingly recognised in Britain over the past 30 years, are very much less common. In the Prince of Wales Hospital only 38 children were admitted in the three year period 1984–7 suffering confirmed or strongly suspected non-accidental injury,[52] and I have no reason to believe that this was then anything other than an accurate reflection of the situation throughout Hong Kong. Most of the abuse was physical, and related predominantly to the discipline of older children (in our study only eight were under 5 years old), exacted chiefly for disobedience or misconduct at home. Child beating was sometimes viewed an acceptable practice. There was only one possible instance of sexual abuse. Many children in whom physical abuse was diagnosed had been born in Hong Kong, sent to China to be brought up by relatives only to return unknown to the parents who in turn failed to cope with stresses posed by a young child rejoining the family.

An appropriate comparison to this experience in Britain is in a 1990 paper from Leeds, population of about 750 000 (fewer than the one million or so population then served by the Prince of Wales Hospital), where between 1985 and 1988, 769 children with physical abuse and 949 with sexual abuse were diagnosed.[53] I am not naive enough to deny the possibility that the real incidence of child abuse in Hong Kong could be more than it gave the impression of being (especially perhaps in the massive housing estates in the New Territories where many young families are now being housed, many miles away from their families in the older urban areas of Hong Kong and Kowloon). But even allowing for this possibility it was nowhere near the magnitude it is now in Britain. But why? A very large number of families live in extremely overcrowded living conditions that would not be tolerated in this country, even in the most disadvantaged council estate. Paradoxically perhaps might 'opportunities' for abuse be less? The extended family is still very strong in Hong Kong with tremendous support given by other family members to mothers and young children who are highly cherished and valued; this could be preventing abuse. There are virtually no unmarried mothers, few teenage pregnancies, and almost full employment; these are factors that could also provide an umbrella of protection.

Enuresis and *encopresis*, in this country often considered social and behavioural problems, were seen much less often in outpatient and maternal and child health clinics. A community study in 1987 in Shatin of 2500 children aged 3–7 attending normal kindergardens and primary schools revealed that 84%, 98%, and virtually 100% of the children were reported by their parents to be dry at 3, 6, and 7 years respectively.[54] This compared then with prevalences from multiple data on children from Britain, western Europe, Australia, and North America between 1956 and 1969 of 68%, 84%, and 89% of children at similar ages being dry at night.[55] I am still curious why bed wetting is such an uncommon problem there: adverse environmental factors, including unsatisfactory housing, have been quoted as *unfavourable* variables in militating against successful treatment of bed wetting.[56]

Sporadic *infectious diseases* occurred and affected children were usually referred to the single Infectious Disease Unit in Princess Margaret Hospital in Kowloon. The most common communicable diseases were viral hepatitis and bacillary dysentery, resulting usually from food contamination. With impressive immunisation uptakes, rates varying from 88% to 99% in 1988–9, outbreaks of measles and whooping cough were exceedingly rare. I cannot also recall seeing or hearing about about any child with a serious complication of pertussis immunisation. *HIV* infection was confined to the haemophiliac population: in 1987, 40% of haemophiliac children possessed the HIV antibody (Dr N K Leung, personal communication). Perinatally acquired HIV infection had yet to be described in Hong Kong when I was there.

One very interesting feature given the high population density of urban living in Hong Kong was the virtual absence of *meningococcal meningitis*. *Haemophilus influenzae* was the commonest cause of bacterial meningitis. Of 61 patients aged 4 days to 11 years with bacterial meningitis admitted to one of the paediatric units at Princess Margaret Hospital between 1979 and 1985 there was not one case of meningococcal meningitis (Dr N K Leung, personal communication). Our experience in the Prince of Wales Hospital mirrored this, not one case of meningococcal meningitis being diagnosed in 1984–9. Between 1986 and 1988 there were only 14 notified cases of 'cerebrospinal meningitis' and meningococcal infection in the whole of Hong Kong, adults and children combined.[57] Reasons for the extremely low incidence of meningococcal disease are not known. Might it be crowded living conditions from birth produce from a very early age a protective antibody response in the whole population?

I would like finally to turn to some disorders that impressed me as having an incidence that showed no obvious differences between west and east. *Acute respiratory tract infections*, of upper and lower respiratory passages, were very common reasons for hospital admission. Audit of admissions to the paediatric wards of the Prince of Wales Hospital in 1984–8 showed lower respiratory tract infections accounting for 41% of admissions.[38] In recent years, and in common with many other countries, there has been reported in Hong Kong an increased prevalence of asthma with many more children requiring hospital admission in recent years.[58] *Febrile convulsions* were as common. *Urinary tract infections* were also much the same and presented in the usual way. *Normal variant short stature* was as much a problem but without the 'indulgence' of being able to treat these children with growth hormone. *Neuromuscular disorders* and *neurodevelopmental handicap* gave an impression of being no less common than in Britain, but exact statistics are not available. As paediatrician to a school of nearly 300 severely mentally handicapped children where I used to conduct weekly 'primary care' clinics and was responsible also for the continued care of the children, I did not discern any obvious difference in the range of the causes of handicap. Some of the most distressing children were orphans who at some stage had been labelled as mentally handicapped, not for any obvious physical reason but as a consequence of abandonment, lack of care and stimulation, and behavioural disturbance acquired through their own emotional conflicts during passages between orphanages and other care centres and institutions. Disturbed they might be, under achieving their potential they undoubtedly were, but mentally handicapped they were not. For as long as this label remained around their necks the solution of their problem through adoption was difficult. Over the years I was encouraged to find fewer of these so labelled and some normal kindergardens had begun to accept these children.

In recent years the problems of the *chronic multiple handicapped child* have become increasingly a concern in Hong Kong. For too long tucked away out of sight these children are now being recognised for what they are and for what they need. But there was still too little awareness of the multiple physical, educational, behavioural, and social problems of these children. Hopefully the much greater exposure now being given to the current generation of medical students will reap rewards in future years to improve the outlook for these children.

Conclusion

Textbooks used in Hong Kong are written by paediatricians in western countries with often little regard for geographical variations in the pattern of illness. The fascinating variations that gradually unfolded in the patterns of illness in the Chinese children of Hong Kong came therefore to have important repercussions beyond their simple biological interest. Undergraduate and postgraduate teaching had to emphasise these variations to be meaningful and relevant.

There is another relevance to paediatricians in general. The return of Hong Kong to the sovereignty of China in 1997 will lead to a continuing increase in the numbers of young Chinese families coming to live in western countries, most notable being the USA, Australia, New Zealand, Canada, and Britain. The health needs of their children need to be understood if they are to be suitably provided. I would like to think that some of my observations will help in this understanding.

I thank my many friends and professional colleagues in Hong Kong who over the years helped me gain a balanced perspective of the clinical problems of Chinese children culminating in these final impressions If any misperceptions and inaccuracies have crept into the text I am solely to blame. For these I apologise

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PERSONAL PRACTICE

Chronic fatigue syndrome: a joint paediatric-psychiatric approach

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Prolonged fatigue after an apparent viral infection, occurring sporadically or as an epidemic, has been described over the past 50 years. It has been given various names including Royal Free disease[1] and myalgic encephalomyelitis, but the preferred terms in the medical literature have been postviral fatigue syndrome[2] or chronic fatigue syndrome (CFS).[3] However, the validity of this syndrome as a nosological entity has created a good deal of controversy and remains in doubt.[4]

A constellation of symptoms make up the syndrome. There is fatigue of defined onset that is generally reported to follow a viral illness, often an influenza-like illness or an infection of the upper respiratory tract. The patient experiences profound fatigue with the initial illness and then fails to make the expected recovery, with fatigue that can persist over months or years. Fatigue is defined as a subjective sensation, which the patient often describes as tiredness or weariness and that occurs at rest. These patients also report a clear relationship of fatigue to activity. The term fatiguability has been used to describe the greater than normal fatigue that occurs after physical and sometimes after mental exertion in these patients. A great variety of associated symptoms have been described that include increased sleepiness, dizziness, vertigo, headache, difficulty in concentrating, sore throat, muscle weakness, and myalgia. The majority of patients have some emotional symptoms. There can be irritability and anxiety, tearfulness and depression. The fatigue and associated symptoms are of such severity as to impair significantly normal daily activities. There is a remarkable absence of physical signs and physical investigations fail to detect any organic pathology or current infection to account for the symptoms.

Two main virus groups have been implicated in the aetiology of the CFS: enteroviruses (particularly coxsackie B) and the herpes viruses. There is serological evidence that some cases may follow enterovirus infection,[5 6] or infectious mononucleosis (Epstein-Barr virus).[7 8] However, these findings have not established a specific association with the syndrome and the proposed causal relationship remains doubtful.[9 10]

Considerable psychiatric morbidity has been described in adult patients with CFS,[11] but there has been little to date in the literature about this syndrome in childhood and no systematic research has been carried out. However, an increasing number of children and adolescents appear to have been given the diagnosis in recent years.[12] This has been a cause for concern[13] because of the multiplicity of factors that probably contribute to this syndrome and because of the treatment implications which the diagnosis may carry. The syndrome can be associated with significant absence from school, restricted physical and social activity with some severe cases being housebound or bedbound for prolonged periods. The purpose of this article is to provide a clinical description of the characteristics and management of a series of consecutive cases which were seen by a paediatric liaison team from a child psychiatry department.

Patient selection and assessment

Ten patients were seen consecutively by the child psychiatry liaison team (CPLT), consisting of a consultant and senior registrar in child and adolescent psychiatry and a clinical psychologist, at Paxton House Family and Young Persons Unit, Reading, over a period of 12 months. Eight cases were referred by a paediatrician and two cases by a consultant in another specialty, at the Royal Berkshire and Battle Hospitals, Reading.

A working party with a consultant paediatrician, community paediatrician, consultant microbiologist, and the consultant and senior registrar in child and adolescent psychiatry of the CPLT met regularly to define criteria and draw up a protocol for the paediatric and psychiatric assessment and management of cases of CFS.

The following criteria were defined and all were fulfilled for inclusion in this series:

(1) A definable onset which may have been associated with a viral infection.
(2) Generalised fatigue
(3) A report of easy fatiguability.
(4) One of the following associated symptoms, headache, dizziness, moodiness, or peripheral sensory change.
(5) The symptoms were of sufficient severity to interfere significantly with normal social and school functioning.
(6) After appropriate investigation and consideration of the history by a paediatrician or other consultant there was no detectable organic pathology to account for the symptoms.

Table 1 Patient characteristics

Case No	*Sex*	*Age at onset (years)*	*Initial illness*	*Age when seen by psychiatrist (years)*	*Duration of symptoms before (years)*	*Length of school absence (major part of No of terms)*	*Home tutor*
1	F	13·4	URTI	14·5	1·1	2	Yes
2	F	12·0	URTI	12·9	0·9	2	Yes
3	M	10·3	Gastroenteritis	10·5	0·3	1	No
4	F	12·8	URTI	15·8	2·9	3	Yes
5	F	14·2	URTI	14·6	0·4	0·5	No
6	F	11·8	Viral	12·8	1·1	2	No
7	F	11·4	Glandular fever	16·4	5·0	6	Yes
8	M	14·4	Influenza	15·6	1·2	2	Home and hospital teaching unit
9	F	12·5	Influenza	14·8	2·3	2	Yes
10	F	13·0	Viral	14·0	1·0	0·5	No

URTI=upper respiratory tract infection

(7) Symptoms persisted at least six weeks after onset.

Where psychological elements were considered to be a major contributing factor a referral was made to the CPLT. A psychiatric assessment included individual and family interviews to identify psychiatric disorders and psychosocial factors which could be maintaining illness. The families in the series were remarkably reluctant to accept psychiatric involvement and where possible they were seen initially in a joint interview with the paediatrician or in a paediatric setting.

Patient characteristics

AGE AND GENDER

The children and adolescents in the series ranged in age from 10·5 years to 16·4 years (see table 1) when seen by a child psychiatrist. The mean (SD) age of onset was 12·6 (1·3) years. The mean (SD) duration of symptoms before referral to a child psychiatrist was 1·6 (1·4) years.

There was a preponderance of girls with a female:male ratio of 4:1.

PHYSICAL SYMPTOMS

The patients experienced fatigue to a degree that interfered with their normal routine activities, and also prevented them from entering into leisure activities such as sports. Some found that if they did engage in strenuous activity, such as sports, they would feel increased generalised fatigue for days or weeks afterwards. For example, case 3 played football one afternoon scoring a goal, but was so exhausted after it that he missed the next three weeks of school. Case 4 experienced such profound fatigue that she would spend half of the day in bed.

The patients had a range of associated symptoms, the most common of which were headache and dizziness. Two cases had headaches and one a sore throat of such severity that they required the daily administration of analgesics.

Four patients (see table 2) had symptoms that led to restrictions in physical mobility. This had a gradual onset with myalgia, muscle weakness, arthralgia, or joint stiffness leading to difficulty walking and an abnormal gait. Three of these patients were eventually unable to walk without support and were using a wheelchair, and two were completely bedbound. While bedbound case 7 experienced a sudden onset of total paralysis in her lower limbs. These three patients were so limited in their mobility that they were unable to perform general self care activities such as feeding, bathing, hair washing, and using the toilet unaided. They were admitted for investigation, including a neurological opinion. On examination these patients were found to be able to use muscle groups for one action that they were unable to use for another. The nursing staff observed that the loss of function was not consistent. For example posture and gait would vary with the onlookers and their relationship to the patient. The patient's symptoms or loss of function were often more severe if parents were present and least severe when they were unobserved.

EMOTIONAL SYMPTOMS

Two of the six patients with depressed mood had been treated by their general practitioner with antidepressants with no response. How-

Table 2 Symptoms

Case No	*Symptoms causing physical restriction*				*Emotional symptoms*				
	Difficulty walking and abnormal gait	*Using a wheelchair*	*Bedbound*	*Paralysis of lower limbs*	*Depression*	*Anxiety*	*Dissociative symptoms*	*Weight loss*	*Weight gain*
1	+	–	–	–	+	–	–	+	–
2	+	+	+	–	–	–	–	–	+
3	–	–	–	–	+	–	–	–	+
4	–	–	–	–	+	–	–	–	–
5	–	–	–	–	–	+	–	–	–
6	–	–	–	–	–	+	–	–	–
7	+	+	+	+	–	–	+	+	–
8	–	–	–	–	+	+	–	–	–
9	+	+	–	–	+	–	–	+	–
10	–	–	–	–	+	–	–	–	+

Table 3 Family characteristics

Case No	*Intact family*	*No of children*	*Ordinal position in family*	*Father employed*	*Father professional or managerial*	*Patient's medical history*	*Family medical history*	*Family psychiatric history*
1	Yes	2	1	Yes	No	—	—	Sister with school refusal
2	Yes	2	1	Yes	Yes	Asthma	Treatment with allergist	Mother with depression and anxiety marital disharmony
3	Yes	2	2	Yes	No	—	—	—
4	Yes	1	1	Yes	Yes	—	—	—
5	Yes*	1	1	Yes	Yes	—	Mother with multiple sclerosis	—
6	Yes	2	1	Yes	Yes	—	Mother with diabetes mellitus	—
7	Yes	2	1	Yes	Yes	—	—	—
8	Yes	2	1	Yes	Yes	Marfan's syndrome	—	—
9	Yes	2	2	No	No	—	—	—
10	Yes	4	1	No	No	Asthma	Father with epilepsy, brother with coeliac disease	Father with depression, marital disharmony

*Father had previous marriage

ever, these were not given at a dosage or for a duration that would enable any conclusions about their effectiveness to be drawn. Those patients who had depressed mood were not consistently depressed and they were able to experience pleasure some of the time. None expressed feelings of hopelessness, worthlessness, a sense of guilt, or suicidal ideas.

Case 5 had specific fears as well as generalised anxiety. She had a long history of fear of needles and bats. She then developed considerable apprehension about normal hypnogogic images, and she experienced parts of her body as larger than normal, a symptom of anxiety known as depersonalisation.

Case 7, who developed a sudden paralysis of the lower limbs, had selective amnesia for the event. This was a dissociative phenomenon, that is a narrowing of the field of consciousness, a symptom associated with hysteria.

ABSENCE FROM SCHOOL

All of the patients had considerable absences from school (see table 1). For clarity where a patient missed over 50% of a school term they are considered to have been absent for that term. School absence ranged from half a term to two complete years.

Of the total series, six patients had serious exacerbations of symptoms (reported to be associated with a further viral illness, such as influenza) which occurred shortly after starting a new school term.

INDIVIDUAL CHARACTERISTICS

All of the patients were in the average range of intelligence and none had a history of developmental or learning difficulties, emotional or behavioural problems.

Cases 7 and 8 were noted to have significant difficulties with social relationships with peers. Case 7 was a shy conscientious girl who was 'old fashioned' in her tastes and attitudes and so she did not fit in with the groups at school. Case 8 has Marfan's syndrome and has been unusually tall since the age of 5 years. He felt self conscious and awkward and was teased at school.

FAMILIES

All of the 10 families were intact, that is to say that the biological parents were married and living together with the child (see table 3). In two families there were long standing marital difficulties. None of the families was from an ethnic minority.

PSYCHIATRIC DIAGNOSIS

Great difficulty is encountered when considering psychiatric diagnoses in these patients and no classification scheme is satisfactory. The descriptive term neurasthenia is useful in some cases, particularly case 4. However, this is a term first used in the 19th century and it has been little used more recently.[14 15]

The consideration of depression is particularly difficult as a number of the symptoms characteristics of CFS—sleep disturbance, difficulty concentrating, and decreased energy—also occur in depressive illness. Although six of the 10 patients experienced depressed mood, none meet the *Diagnostic and Statistical Manual of Mental Disorders Third Edition, Revised* (DSM III-R) criteria for the depressive disorders.[16] Similarly none of the patients meet criteria for the specific anxiety disorders. The most useful diagnostic category is somatisation disorder except that many of the criteria are not appropriate to children and adolescents.

Management and the active rehabilitation programme

After physical investigations excluded serious underlying organic pathology the patient and family were reassured, and an explanation of CFS was given recognising the suffering and distress of the patient. Specific psychiatric treatment was given where appropriate, for example cognitive therapy for anxiety in case 8, and dynamic and systemic issues were addressed in individual and family interviews.

An active rehabilitation programme was offered to all cases. This is a behavioural programme of gradual increase in the patients activities in a number of areas including school attendance, leisure, social, and physical activities. The patient and a parent were seen once a week with the aim of rehabilitation in one to three months. Baseline information was first obtained to determine the current level of activity. This information was obtained at interview and with a diary kept by the patient listing all activities and rest periods; this gives valuable details and can be used to measure progress if used throughout the rehabilitation. It is important that the patient has a sense of participation in the programme and they were involved in setting specific goals for increasing activity.

The programme moved from baseline activities in all areas in gradual stages. Direct contact with the school was essential to negotiate a gradual increase in participation in the school timetable. The patient was encouraged to go out for education every day and home tuition was avoided wherever possible. Prolonged illness can lead to social isolation and an increase in social and enjoyable activities provided more positive goals and increased motivation for school return. Physical activity was increased with exercises, outings, and a gradual reintroduction of sporting activities.

In cases where there were symptoms causing physical restriction or the patient had been housebound for some time, inpatient rehabilitation on a paediatric or other medical ward was offered. A similar approach was described by Dubowitz and Hersov in hysterical disorder.[17] This was found to be the setting that was most acceptable to these patients and families, and it offered an enhancement of the programme by the involvement of other professional staff. Nurses, occupational therapists, and teachers were involved in increasing self care, lesiure, and academic activities. A physiotherapist provided exercises and special equipment, including hydrotherapy, to increase physical activity. A detailed active rehabilitation programme was drawn up by a member of the CPLT with specific targets agreed by the patient and the whole team. Pleasurable activities, such as trips out, acted as encouragement for goals reached in other areas. An inpatient admission of two to eight weeks was followed by weekly outpatient appointments to continue the programme until there was a return to normal functioning.

Outcome

Cases 3 and 8 showed gradual improvement with outpatient psychiatric treatment, which included individual and family interviews and a programme of active rehabilitation. At the end of six months case 3 was symptom free and engaging in normal activities. Case 8 was attending college full time at one year follow up. His physical symptoms were much improved but he continued to have some difficulties with social relationships. In case 10 the mother sought psychiatric advice when she noticed that her daughter's fatigue and misery were greatly alleviated during periods spent away from the family. Once the focus was diverted from the patient to the chronic severe marital difficulties her symptoms quickly subsided.

The four patients with symptoms causing physical restriction were offered inpatient treatment. Case 7 made a dramatic recovery when on the third day of her admission the paralysis in her legs suddenly disappeared. After two weeks she was walking unaided and after three weeks doing headstands and fitness training. She remained an inpatient for one month. Eighteen months later she was symptom free and attending college full time.

Case 9 recovered more gradually and was an inpatient for two months but maintained her improvement and was symptom free at follow up six months later.

The occurrence of loss of motor function appeared to improve outcome in these two cases as it brought about a realisation on the part of the parents of the importance of psychological factors and these patients made a particularly good recovery. Case 1 was an inpatient for two weeks and improved considerably but she and her family were not convinced that there was no organic basis for her symptoms and they recurred soon afterwards.

Three of the families (cases 4, 5, and 6) failed to attend a second outpatient psychiatric appointment and case 2 refused inpatient treatment. In these cases the parents were convinced that their child's illness was purely physical in origin and that active rehabilitation would be harmful.

Where the patient and parents accepted treatment, including an active rehabilitation programme, a substantial improvement was achieved in every case.

Discussion

This series illustrates that the children and adolescents who have the symptoms of CFS are an important group upon which the medical profession should focus attention. They may develop prolonged and severely debilitating symptoms, the nature of which may be difficult to interpret as many of the symptoms also occur in psychiatric disorders.

Cartesian dualism, that is the separation of the body and the mind, may be the origin of some of the confusion and controversy surrounding this subject. These cases suggest that the most useful model regarding CFS is a complex interaction of physical and psychological components. A valuable hypothesis is that in the minority of cases where there is a prolonged course or an associated psychiatric disorder that the experience of fatigue is maintained by other psychosocial factors. These psychosocial factors include individual and family factors and wider issues of clinical management and expectation of continuing activity and school attendance.

Possible individual maintaining factors are earlier experience of prolonged illness, poor social adjustment, problems at school, or high expectations of achievement before the illness.

The role of depression in CFS is uncertain. In a study by Wessely and Powell 47% of adult patients with CFS also fulfilled internationally accepted diagnostic criteria for affective disorder, and 25% had other psychiatric diagnoses including somatisation disorder, phobic and generalised anxiety disorders, and conversion disorder.[11] Childhood emotional disorders are less well differentiated than adult disorders, however associated psychiatric disorder may act as a maintaining factor in CFS.

Two relevant concepts in psychiatry illustrate the complex interactions of the physical and psychological. The first is abnormal illness behaviour,[18] which encompasses the range of psychiatric diagnoses that have been given to patients with physical complaints for which no adequate organic cause can be found. These include hypochondriasis, neurasthenia, conversion hysteria and somatisation disorders. Goodyer has shown that hysterical conversion in childhood frequently involves disturbance of gait and lower limb function.[19] Abnormal illness behaviour can occur without physical illness, it may be a prolongation of symptoms originally part of an organically determined disease, or it may accompany an undoubted organic disease. It is as Taylor describes when discussing hysteria, in a different domain from physical illness and it in no way invalidates it.[20] The cases where there was loss of motor function suggest that abnormal illness behaviour can be a very important mechanism in CFS.

School refusal is the second relevant psychiatric concept. This is where the child is reluctant to go to school and remains at home. In many cases there is anxiety about separation on the part of the mother as well as the child. School refusal may follow a period of physical illness. A variant has been described 'the masquerade syndrome' by Waller and Eisenberg.[21] This is school refusal disguised as physical illness. Parents can become intensely involved in the idea of their child's illness, making it impossible for him to go to school. The close connection, in some of our cases, of exacerbations of symptoms with the beginning of a new school term suggests that the mechanisms encountered in school refusal may play an important part.

Family factors are particularly important in the development of psychological disturbance in children and adolescents. Physical and psychiatric illness in other members of the family or marital problems may be important in maintaining illness on the part of the child. The intact professional or managerial high achieving family may increase the risk of a child developing severe or prolonged disabilities. The majority of our patients were from this type of family where they were the elder of one or two children. This may be interpreted as a referral bias. However, one can speculate that these families have a high investment in their children and that there is pressure to achieve on either the part of the parent or the child. There may then be an inability to accept reduction of energy and performance after illness. These families may also have difficulty in negotiating the issues of growing independence in adolescence, which would be particularly relevant with an elder female child.

Parental beliefs appear to be of vital importance in CFS. These families frequently hold firm beliefs in the purely physical nature of their child's difficulties. Families are often exposed to the literature of the ME [Myalgic encephalomyelitis] Association and the Action Campaign These associations give a view of a single disease entity with a purely viral cause, where physical exertion may be harmful and must be avoided, and where rest is the recommended treatment. Rest may act in a circular way so that after rest when physical exertion is attempted normal physiological sensations are interpreted as a relapse. The beliefs of a parent can be so prominent that 'myalgic encephalomyelitis by proxy' possibly a variant of 'Munchausen syndrome by proxy' has been described.[22]

The individual should be seen in the context of his psychosocial predicament.[20] As well as individual and family factors this includes wider social influences. Continuing medical investigation or contradictory recommendations from the medical profession, who often find themselves unable to offer effective solutions, may be maintaining factors. Parents may become very involved in their child's illness and this may even inadvertently prolong or exacerbate the situation. The families may turn to 'alternative' treatments where their experience of illness is validated and complex treatments including restricted diets and numerous vitamin and mineral supplements may be recommended. Home tuition may also validate illness behaviour and should be avoided except as part of a rehabilitation programme.

In conclusion it is proposed that the combined approach of a paediatrician and a child psychiatrist is adopted. This is of particular value in the difficult process of engaging the patient and family in treatment. In those cases where treatment was refused or of limited success, there was a continuing belief in a purely organic basis to the symptoms. It is important that psychiatric referral is not delayed in those patients where there are significant emotional factors, failure of progress in treatment, or a prolonged course. An active rehabilitation programme, in conjunction with specific psychiatric treatment where appropriate, when accepted is an effective treatment approach.

There is a need for systematic research into this fascinating condition in childhood and adolescence for the establishment of internationally accepted criteria, data on incidence, and outcome studies. Criteria for adults, Holmes *et al* for example,[3] require symptoms for at least six months. This is almost certainly too long for children where a period of two months would be more appropriate.

Childhood and adolescence is a time of enormous physical, emotional, and social changes with considerable implications for personality development. These children are in danger of profound interference with normal psychological development and chronic dysfunction. They must not be left in a no man's land between paediatrics and psychiatry.

I thank Dr Pieter van Boxel and Penny Spinks of the Child Psychiatry Liaison Team, Paxton House; and the paediatric department of the Royal Berkshire and Battle Hospitals, Reading

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Prolactin and seizures

I've heard of *post hoc ergo procter hoc* but never before of *pre hoc ergo procter hoc*. To the best of my knowledge the use of serum prolactin measurements to distinguish between true and false fits was first described by Michael Trimble in the *British Medical Journal* in 1978.[1] A recent report from Israel (Nathanel Zelnick and colleagues, *Pediatrics* 1991;**88**:486–9) is the latest of several to confirm that a rise in serum prolactin concentration occurs after generalised tonic-clonic seizures and not after febrile convulsions, hysterical attacks, breath holding, or syncope. After complex partial seizures there may be a lesser and less reliable rise in serum prolactin and with other kinds of seizure the test is not helpful.[2] The Israeli workers refer to several papers published between 1980 and 1987 and say that they led to Trimble and others suggesting that the phenomenon could be helpful in distinguishing between epilepsy and non-epilepsy.

Does precedence matter? In the ultimate analysis I suppose not but it's as well to get things right if only to keep the historical record straight.

ARCHIVIST

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Archives of Disease in Childhood 1992; **67**: 556–559

PERSONAL PRACTICE

Human milk banking at Sorrento Maternity Hospital, Birmingham

S E Balmer, B A Wharton

Milk banking refers to the collection, processing, and storage of human milk and feeding that milk to someone other than the donor's own baby. In some ways it is a more simplified and less controlled form of wet nursing. Similarly it has had periods of favour and times when it was unpopular, as happened to wet nursing in the 15th century because of the spread of syphilis.[1] Currently milk banking is going through a phase of uncertainty. One of the reasons is that babies have become infected with the HIV while breast feeding.[2–5] The virus has also been found in cell free breast milk.[6] The second reason is that there are now commercially available formulas designed especially for the low birthweight infant. These formulas provide enough energy and other nutrients to meet the expected growth of a preterm baby had it still been 'in utero' (with a few exceptions such as calcium). Recent studies comparing banked breast milk with a low birthweight formula confirm this difference in growth,[7] and perhaps more importantly have shown that the developmental quotient at 9 months was 0·25 standard deviations lower in those receiving donor milk.[8]

For these and possibly other reasons there are many fewer milk banks than previously. In 1981 the Department of Health and Social Security (DHSS) listed 19 'established milk banks in Great Britain'.[9] To our knowledge only six are now functioning.

History

The first milk bank was set up in Vienna in 1900 and 10 years later another was organised in Boston, USA. The first milk bank in the UK was opened at Queen Charlotte's London. After the second world war milk banks designed to supply a service to other hospitals were set up, notably the Sorrento Maternity Hospital in Birmingham, St Davids at Cardiff, Bristol, and later Leicester and Liverpool. In 1973 there were five large 'commercial' milk banks in Britain at Queen Charlotte's in London, St David's in Cardiff, Sorrento in Birmingham, Southmead in Bristol, and Royal Alexandra in Brighton. Now only the Sorrento Maternity Hospital regulary supplies milk to other hospitals.

The human milk bank in Birmingham was established in 1950 at Birmingham Children's Hospital and transferred to Sorrento Maternity Hospital in 1955.[10] In 40 years it has had over 10 000 donors and collected and distributed approximately 50 000 litres of breast milk; currently it processes about 700 litres per year. It supplies milk to the neonatal unit at Sorrento Maternity Hospital, other hospitals in the West Midlands, and elsewhere outside the region.

The use of donor breast milk

There are many well known theoretical immunological advantages to breast feeding, particularly the anti-infective properties and reduction in allergic reactions.[11–12] Work from Dundee has shown a reduction in gastrointestinal illness and admission to hospital in those breast fed for at least 13 weeks.[13] Also the large multicentre trial based in East Anglia found that preterm babies fed infant formulas were 6–10 times more likely to develop necrotising enterocolitis than those fed breast milk and pasteurised donor milk seemed to be as protective as maternal milk.[14] A feeding study in India has shown that pasteurised breast milk still confers protection from infection.[15]

It is often thought that banked breast milk has considerably reduced immunological factors because of the heating it undergoes during pasteurisation. Studies have shown that the time and temperature of pasteurisation is important in determining the content of lactoferrin, lysozyme, and immunoglobulin in pasteurised milk. Holder pasteurisation is for 30 minutes at 63°C (designed to kill *Mycobacterium tuberculosis*) but breast milk is mostly contaminated with skin commensals which are more susceptible to lower temperatures. Table 1 shows that a reduction of temperature to 56° improves the content of protective factors.[16–20]

Therefore despite the disadvantages of slower overall growth and development with prolonged use there are a number of inherent advantages in the use of expressed breast milk in the short term for the ill newborn baby. The custom here and in many other units has been to use banked breast milk only in the very low birthweight baby and then only during the first week or so while achieving gastrointestinal tolerance. Thereafter as the accent of care changes from 'survival' to 'rehabilitation and catch up growth', a normal or low birthweight infant formula is gradually substituted. One other feature of the large East Anglian studies was the better gastrointestinal tolerance of banked breast milk compared with a low birthweight formula during

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Table 1 Reduction of immunological factors in breast milk after pasteurisation at two temperatures in different centres (reduction as % of level in untreated milk)

	63° for 30 min				*56° for 30 min*
	Reading[16]	*Oxford*[17]	*Cardiff*[18]	*Stamford, USA*[19]	*Oxford*[20]
Lactoferrin	65	NT	57	NT	10
Lysozyme	Nil	36	24	NT	Nil
IgA	22	21	Nil	33	10

NT=not tested

the first week or so of life.[21] It is our impression that immediate but short term use of banked breast milk has often prevented the need for parenteral nutrition because enteral feeding is rapidly established. We are aware that a number of colleagues use banked breast milk as the first enteral feed after neonatal bowel surgery.

Apart from its use with the ill newborn an occasional use is for severe gastrointestinal food intolerance. However as the affected infants are larger than newborns the volume demand is greater and has occasionally placed strains on supplies.

Screening of donors

Donor mothers are asked about their medical history with particular reference to infectious diseases. Milk is not accepted from mothers who are hepatitis B carriers or have antibodies to syphilis. Donors are asked not to give milk to the milk bank if their baby becomes ill at any time.

Donors are also questioned about any medication that they are receiving. There are very few drugs that prohibit a mother from breast feeding her own fit healthy baby but as donor milk is being fed to sick infants of other mothers, more precautions are taken. We do not accept milk from mothers (a) who are regularly receiving any drugs other than the contraceptive pill or the occasional analgesic such as aspirin or paracetamol; (b) who have received antibiotics in the previous 48 hours; and (c) who admit to smoking more than 10 cigarettes a day.

Each mother must have a refrigerator or freezer so that her milk can be stored frozen as the mothers are visited only once every 10 days.

HIV antibody testing of donors

Evidence suggests that breast milk might be involved in the transmission of HIV as breast fed babies of recently infected, mothers have developed AIDS.[2–5]

In accordance with the directive from the DHSS all donors at Sorrento Maternity Hospital are now screened for HIV antibodies.[22] The necessity for a blood test is explained to every mother when she first contacts the milk bank about donating milk. Only four mothers (out of 470) have refused to be tested. When the milk bank nurse visits the mother for the first time they are given a form (similar to that given to blood donors) which lists the high risk groups for AIDS and asks them not to offer their milk if they could fall into any category. Each mother gives written consent to be tested for HIV antibodies. Should a donor be HIV positive, arrangements for counselling are made. All mothers are bled in their own homes to save them any inconvenience. Often milk is donated before we know the results of the HIV antibody test and this milk is stored in a separate freezer until the result is known.

The Association of British Insurers have provided us with a leaflet explaining that mothers applying for life insurance will not be affected by having had an HIV antibody test as part of our donor screening programme. Mothers who are expressing milk for their own babies on the neonatal unit are not tested for HIV antibodies. However if they have a surplus in excess of the requirements of their own baby which could be used for another baby, that mother is also tested.

Collection of breast milk

Donor mothers are provided with a hand breast pump *not* a breast reliever (a bicycle horn pump). Careful instructions on how to clean and sterilise the pump are provided in a small booklet. Breast relievers are not suitable for collecting banked breast milk because they are difficult to clean and sterilise. The hand pump used is made by Egnell Ameda (Taunton), costs approximately £10, and most mothers find it satisfactory. Hand expression is the cleanest method of expressing milk but most mothers prefer to use a hand pump. If a mother is expressing milk for her own baby on the neonatal unit she is supplied with an electric pump (Egnell Ameda, Humolactor). This makes it easier to sustain lactation as to some extent it mimicks the stimulation of normal suckling.

Mothers are also supplied with a shell to collect 'drip' milk which leaks from the opposite breast to the one being suckled. Mothers are advised only to collect drip milk while feeding and not at any other time, so that the milk supply is not increased by the pressure of the shell on the breast for too long a period. Drip milk is foremilk with a lower fat content and thus lower energy content than expressed or hind milk. We therefore encourage the collection of expressed milk, but do not exclude any drip milk. Milk is transferred from the breast pump to Axicare breast milk bottles (Colgate Axicare, Windsor; 120 or 240 ml size). The bottles are reused and are not sterile. In between use all bottles are thorougly cleaned in a washing machine and dried, which we have found adequately disinfects them.

All milk is stored in the donor's freezer at −20°C or in the freezer part of her refrigerator at −5°C until it is collected by the milk bank staff. Mothers are visited at home by the milk bank nurses every 10 days to collect the frozen milk and deliver a fresh supply of bottles. While on the 'milk round' the nurses put all bottles of frozen milk into a cooler box to ensure that the milk remains frozen on its journey back to the milk bank.

Microbiological quality control

Each bottle of milk supplied by the mothers is examined bacteriologically. The day before the milk is pasteurised it is thawed at room temperature for three hours and 10 µl milk (using a standard loop) is inoculated on to CLED agar (cystine–lactose–electrolyte deficient, CM423 Oxoid) and incubated at 37°C overnight. The milk is kept at 4°C overnight.

There are no accepted microbiological criteria for the control of donor milk. The DHSS report *The Collection and Storage of Human Milk* described methods but left criteria 'to the microbiologist concerned with the setting up of each individual milk bank'.[9] The microbiological criteria used at the Sorrento Maternity Hospital for accepting milk for pasteurisation are:

(1) Milk with counts of less than 10^3 colony forming units (cfu)/ml is used regardless of the organisms present.

(2) Milk with counts of more than 10^5 cfu/ml is *not* used.

(3) If milk has counts between 10^{3-5} cfu/ml it is only used if the organisms are skin commensals—for example, *Staphylococcus epidermidis*, viridans streptococci, and diphtheroids. Milk is not used if it has counts of more than 10^3 cfu/ml of *Staphylococcus aureus*, any Gram negative rod (lactose fermenting and *Pseudomonas* sp), β haemolytic streptococci or *Streptococcus faecalis*. These criteria are similar to those recommended by the milk bank at King's College Hospital, London.[23 24]

These criteria are necessary because pasteurisation is ineffective if milk is heavily contaminated with micro-organisms. A linear relationship exists between the logarithm of the number of surviving organisms at a given temperature and the length of time for which the organisms are exposed to that temperature. Although heat treatment will kill most bacteria present in milk, the toxins produced by some bacteria are not necessarily destroyed by heat. It is therefore advisable to eliminate milk contaminated with any toxin producing organisms such as *Escherichia coli* and *S aureus*. Theoretically lipases, proteases, and decarboxylases that are released by certain micro-organisms such as Gram negative bacilli, faecal streptococci, and *S aureus* during pasteurisation could cause undesirable effects in the newborn.[25]

All acceptable milk is strained through sterile muslin to remove any hairs or bits of fluff from donor's clothes. The donor milk is then pooled. Only milk expressed by a mother for her own baby in the neonatal unit is kept separately. Pooled milk is transferred to 250 ml glass Winchester bottles for pasteurising.

A further check of the bacterial content of the raw pooled milk is then made by inoculating another 10 µl loop on to CLED agar. This check ascertains that milk has not become contaminated with unacceptable organisms (see above) during straining and pooling. If milk had become contaminated the whole batch would be discarded.

Table 2 Microbiological analysis of 5872 bottles of milk collected during one year

	No (%) of bottles
Total counts of organisms (cfu/ml)	
$<10^3$	1934 (33·0)
10^3	333 (5·7)
10^4	2376 (40·5)
10^5	990 (16·9)
$>10^5$	239 (4·1)*
Organisms present	
S epidermidis	2809 (47·8)
S aureus	232 (3·9)
Coliforms	688 (11·7)
Enterococci	22 (0·4)

*This milk is rejected, milk with counts of 10^{3-5} may be rejected depending upon the organisms found—see text

Table 3 Chemical analysis of breast milk (per 100 ml)

	Donor milk from 75 batches, each batch containing milk from 5–20 donors		*Mature human milk (DHSS)*[28]
	Mean (SD)	*Range*	
Sodium (mg)	17·0 (3·9)	11·0–34·0	15·0
Fat (g)	2·2 (0·3)	1·6–3·4	4·2
Protein (g)	1·2 (0·1)	1·0–1·4	1·3
Lactose (g)	7·2 (0·2)	6·8–8·8	7·0
Calculated energy (kJ)	217		293

Contamination of milk

About 10% of bottles of milk supplied by mothers are discarded as being too contaminated for use. The detailed microbiological analysis for milk collected during one year is summarised in table 2. Milk with very high counts of bacteria is usually contaminated with coliforms and often there is more than one type of bacterium present in each bottle of milk.

Pasteurisation

All milk is pasteurised at 56°C for 30 minutes in a custom built pasteuriser (Scott Weston) and rapidly cooled to 10°C at the end of the cycle. The model we use is no longer commercially available but is very similar to the Colgate Axicare CM80. The whole cycle (time and temperature) is recorded on a chart that is kept for reference.

All milk should be at room temperature immediately before pasteurising because pasteurising is not effective if the temperature has to be raised considerably during the cycle.[26]

Most skin bacteria are killed and viruses including HIV are inactivated at 56°C for 30 minutes.[27] The efficacy of pasteurisation is checked by including a test bottle in each batch. The test bottle is a 250 ml Winchester containing water in which a small bottle containing 5 ml of raw milk is submerged. After pasteurisation 0·2 ml milk from that sample is inoculated on to two blood agar plates, one is incubated aerobically and the other anaerobically at 37°C for 48 hours.[9] A batch of milk is not used until a report of no growth for this sample is received from the laboratory.

After pasteurisation all milk is stored frozen until use when it is defrosted either in a refrigerator or at room temperature. Pasteurised breast milk can be stored frozen for up to six months. Each batch is numbered and it is recorded which batch is fed to each baby or sent to other hospitals in accordance with DHSS recommendations.[22]

Chemical analysis

Each batch of pasteurised milk is analysed for its chemical composition, free of charge by Farley Health Products. A 70 ml sample with bronopol milk preservative (2-bromo-2-nitropropan-1, 3-diol) added to it is sent through the post. The contents of protein, fat, lactose, and sodium are shown on the label of each bottle of milk that leaves the milk bank. The values obtained during one year are shown in table 3.

Storage and despatch

Sorrento Maternity Hospital supplies milk to other hospitals in the Birmingham area on a regular basis. If hospitals further afield require milk, each bottle is wrapped in bubble polythene, packed in cardboard boxes and despatched via the Red Star parcel service or British Rail.

Funding

The Sorrento milk bank is run in conjunction with the milk kitchen for the neonatal unit and is funded by the South Birmingham Health Authority. The staff for both the milk kitchen and milk bank include a microbiologist, part time sister, two part time nursery nurses, a nursing auxillary, and a domestic assistant. The milk bank has its own vehicle to enable the staff to visit the mothers in their homes. All milk is sold at currently £15 per litre either back to South Birmingham Health Authority or to any other authority requiring the milk.

Conclusion

A number of milk banks closed after the DHSS advised screening every donor for HIV[22] because it was felt mothers would not find it acceptable. There were also doubts about the suitability of donor milk for preterm babies. We have shown that mothers are cooperative in being screened for HIV, and it has not created the problems that we had anticipated. There are still arguments for feeding the sick preterm newborn baby with breast milk during the first weeks or so of life. In our opinion therefore milk banking should be continued. We do consider that some degree of both microbiological and chemical monitoring is necessary and the methods used in the Sorrento milk bank have been described.

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Archives of Disease in Childhood 1992; 67: 560–564

CURRENT TOPIC

Paediatrics in the accident and emergency department

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When the National Health Service began in 1948 many hospitals, large and small, had casualty departments. These were usually run by experienced and dedicated nursing staff in often inadequate accommodation. Self taught clinical assistants were in overall charge but had inexperienced, often poorly supervised junior medical staff. The departments treated patients, including children, with a wide range of trivial or serious illness and injury.

In 1962, the Platt committee recommended that the renamed 'accident and emergency' departments be under the direction of orthopaedic surgeons.[1] However, this solution was not generally successful and in 1971 the Joint Consultants Committee under Sir John Bruce suggested that a new type of specialist be created, namely consultant in accident and emergency medicine.[2] There are now over 200 such specialists in England and Wales.

Range of paediatric problems in accident and emergency medicine

Little national or regional data are regularly gathered about children's accident and emergency attendances. Most districts record the number of child attenders under the age of 16 years, but no other details. Our knowledge of children's problems in accident and emergency is therefore mainly based on small local studies.

It is estimated that between 20% and 25% of the child population is treated annually at accident and emergency departments amounting to between 2 and 2·5 million children a year in England and Wales.[3] In a typical health district with a large district general hospital whose accident and emergency department has 60 000 new attenders per year, 20–30% (15 000 to 20 000) will be children.

The largest group of child attenders are those with trauma. Most of these have minor injuries. The commonest minor trauma is a head or facial injury in a child under 5 years old (B M Phillips, unpublished observations). Lacerations, simple fractures and sprains, animal bites, ingestions and foreign bodies, and burns and scalds, comprise most of the remainder of the minor trauma problems.

It is estimated that at least 15% of child attenders have medical conditions. These range from the seriously ill child with convulsions, collapse, or respiratory difficulty to patients who have conditions which could be treated by their general practitioner. In this latter group most are children with the common acute illnesses of childhood, especially respiratory and gastrointestinal infections. A minority have long standing conditions that have caused sudden concern, for example, recurrent abdominal pain or headaches. Children under 5 years and especially those under 2 years predominate in the medical attenders.[3]

A small percentage of patients have non-traumatic surgical diseases such as irritable hip, Perthes' disease, appendicitis, hernia, etc. Some children, usually adolescents, attend with symptoms related to drugs, alcohol, or solvent abuse or after self harm.

Areas of special concern in child attenders at accident and emergency departments

MAJOR TRAUMA

Trauma is the leading cause of death in children over the age of 1 year in the developed world. In England and Wales each year approximately 700 children die and about 10 000 are permanently disabled as the result of accidents.[4]

In 1988, the Royal College of Surgeons of England's working party on the management of patients with major injuries reported that of 1000 deaths in all age groups from trauma (which were assessed retrospectively), 20% were deemed to have been preventable if optimal treatment had been provided after the accident.[5] Although the report does not make clear how children in the study fared compared with adults, it is likely that many deaths in childhood caused by trauma are preventable. A similar study in the United States considered that 53 out of 100 consecutive paediatric trauma deaths were potentially preventable with optimal treatment.[6] A study of deaths in children with head injury from Newcastle identified 42% of 255 deaths as being possibly or probably avoidable with better treatment after arrival in hospital.[7]

The poor outcome probably arises from the relative inexperience and lack of training of staff in most hospitals when it comes to treating the severely injured child. Although trauma is the commonest cause of death in childhood, individual staff are likely to treat only one or two such patients a year. However, severely injured children urgently need the skills of trained and experienced accident and emergency staff, anaesthetists, and surgeons. The child requires rapid stabilisation with airway, ventilatory, and circulatory support and transfer to a unit experienced in paediatric trauma management. Paediatricians will recognise parallels here with the needs of the very small or very sick neonate.

The Royal College of Surgeons working party recommend the setting up of American style trauma centres in each region. In such a centre, specialist surgeons, anaesthetists, and operating theatres would always be available for the treatment of seriously injured patients. The working party recognised that severely injured children require paediatric facilities including paediatric surgeons, anaesthetists, and intensive therapy. It recommended that, where feasible, a major paediatric facility be part of the hospital containing the trauma centre. However, the working party considered it appropriate that injured children be transferred from the trauma centre to the children's hospital if the two were not on the same site. The Department of Health has recently funded a pilot centre to study the feasibility of trauma centres in the UK.

THE SERIOUSLY ILL CHILD

Early recognition and prompt, effective treatment of the seriously ill child in the accident and emergency department is vital, especially when the children's department and therefore the paediatric team is on a different site. These aims can be achieved only when the senior house officer in the accident and emergency department has in-post paediatric training and where trained and experienced middle grade staff are readily available.

CHILDREN BROUGHT IN DEAD

Children who have been the victims of a fatal accident or who have been found suddenly and unexpectedly dead are usually brought to the nearest accident and emergency department. Infants under 1 year old make up the majority of the latter group. Sensitive, caring, and supportive management of the family at this time will have a profound and prolonged positive influence on the response of the family to the death in the long term. Doctors, nurses, and social workers must be trained in these skills.

CHILD ABUSE

The problem of child abuse runs through the whole range of paediatric conditions treated in an accident and emergency department. Guidelines for recognition and management are necessary for this often complex situation. Clear lines of referral to senior paediatric staff should be agreed for children who present to the department with worrying injuries. However, the assessment of the child and his or her circumstances by the paediatrician and social worker is not best undertaken in the accident and emergency department unless there is a specially designated and staffed area for this purpose. The privacy and confidentiality required in these circumstances cannot always be maintained in a busy department.

INAPPROPRIATE ATTENDERS

Management of the inappropriate attender is a concern in all accident and emergency departments. An inappropriate attender is usually regarded as one whose condition is neither a recent accident nor an emergency and who would normally seek medical advice from his general practitioner. Many accident and emergency departments have a policy of referring such patients back to their general practitioner for treatment but this policy is not applied to children.[8]

In an unpublished study in a paediatric accident and emergency department, parents said it was not the unavailability of general practitioners that prompted them to bring their child to the paediatric accident and emergency department but their perception that the child's illness was an emergency and their belief that superior skills lay within the children's hospital (B M Phillips, unpublished observations). The accident and emergency department can be regarded as a 'safety net' where parents may obtain primary health care for their children if, for whatever reason, they have failed to obtain it elsewhere. In the inner cities there is a higher proportion of such child attenders compared with rural or suburban areas.

Paediatric accident and emergency departments

The joint statement on children's attendances at accident and emergency departments produced in 1988 by the British Paediatric Association, the British Association of Paediatric Surgeons, and the Casualty Surgeons Association (now the British Association for Accident and Emergency Medicine) recommends that paediatric accident and emergency medicine should develop as a specialty with the aim of establishing consultant posts in paediatric accident and emergency medicine in children's hospitals.[3] The statement recommends that there should be at least one paediatric accident and emergency unit in each region or large urban area based on a children's hospital or in a large accident and emergency unit within a hospital associated with a university department of child health.

There are at present five consultant led paediatric accident and emergency departments in England and Wales. In addition, there are two in Scotland, one in Northern Ireland, and two in the Republic of Ireland. These are all based on children's hospitals. In addition there are a few accident and emergency departments in children's hospitals with paediatric consultant supervision. Paediatric accident and emergency departments provide a service for the surrounding population and also attract a small number of additional 'medical' paediatric cases from further afield so that medical attenders comprise approximately 25% of the workload of these departments.[3]

The rationale for the existence of paediatric accident and emergency departments is:

- As a teaching and training resource for medical, nursing, and other staff.
- For research into the epidemiology and pathology of acute illness and injury.
- For the development of management strategies for acutely ill and injured children.

CASUAL ATTENDERS IN PAEDIATRIC UNITS

In addition to identifiable paediatric accident and emergency units, some paediatric units operate an 'open door' policy for self referred patients, both old and new, to be treated in the unit's admissions department. This practice is only safe if resuscitation facilities and skills are available.

Proposals for the future development of paediatrics in district accident and emergency services

Several of the following proposals have already been put forward in the joint statement of the British Paediatric Association, the British Association of Paediatric Surgeons, and the Casualty Surgeons Association[3] and in the quality review produced by the National Association for the Welfare of Children in Hospital.[9]

PHYSICAL FACILITIES

It is proposed that:

- The accident and emergency department should be on the same site as the paediatric inpatient services so that experienced paediatric help will be readily available.
- The department should be clearly visible to families seeking treatment and should be well signposted.
- It should have a separate play and waiting area for children of sufficient size to cater for the average peak demand, not forgetting that many children are accompanied by siblings, therefore suitable toys and books for different ages groups should be provided.
- Consulting rooms should be big enough to accommodate the child, parents, and any siblings who have had to be brought in the emergency situation.
- There should be a separate children's treatment room suitably decorated and equipped.
- Children's waiting, play, and treatment areas should form a recognisably separate but contiguous subunit in the main department.
- There should be a private room for distressed parents or for private interviews with parents.
- There should be child size as well as adult toilet facilities and a nappy changing area.
- There should be a private area for mothers who are breast feeding.
- Enclosed areas are provided: they are more appropriate for children as they prevent children wandering. Sound attenuation is useful in both directions.
- Children's resuscitation facilities should not be separate from the main resuscitation area or there may not be sufficient staff to man both areas—however, one resuscitation bed should be for children with paediatric equipment and drug dosage protocols easily accessible.

MEDICAL STAFF TRAINING

Newly appointed senior house officers should have in-post training, which includes cardiopulmonary resuscitation in childhood, the initial management of the seriously ill or injured child, management of common paediatric problems, and recognition of child abuse.

They should be able to ventilate a child by bag and mask for a short period and should be trained in techniques of venous access including intraosseous infusion.

In-service training should continue on a regular basis. Attendance at an advanced cardiac or advanced trauma life support course would be very useful. There are plans to hold advanced paediatric life support courses in the UK similar to those in Canada and the United States.

CONSULTANT TRAINING

At present the Specialty Advisory Committee (SAC) on higher medical training requires only a minimum of three months paediatric experience before accreditation as a consultant in accident and emergency medicine. However, we suggest that a year's paediatric experience would be preferable to most candidates for such posts. The experience might appropriately be gained in a six months' paediatric senior house officer post at a district general hospital with a further six months of experience in paediatric specialities in the registrar or senior registrar years. These specialties should include intensive care and anaesthetics. A post in a paediatric accident and emergency department would also give valuable experience. In some large accident and emergency departments in district general hospitals where more than one consultant is appointed, we would recommend that one of the consultants should have a special interest in paediatric accident and emergency medicine with some additional training.

There are a few consultant posts in paediatric accident and emergency medicine. These are based in children's hospitals. Such departments treat children with a wide range of paediatric problems, including those pertinent to the hospital's tertiary specialist departments. Training for such posts falls under the scrutiny of both the SAC in paediatrics and the SAC in accident and emergency medicine. Discussions continue about the detailed content of such training programmes.

NURSING STAFF

It is proposed that:

- There should be one registered sick children's nurse on each shift.
- All nursing staff should have training in paediatric basic life support, drug administration, and equipment used for children.
- Further training should be available for nurses who wish to undertake extended roles—for example, plastering, suturing, intubation and intravenous access, and ordering *x* rays.
- Some departments develop the role of a clinical nurse practitioner who could treat patients with minor illness or injury without medical supervision.
- A paediatric district nurse is available to provide follow up in the community: this may avoid some admissions to hospital.
- There is liaison with the health visitors on all child attenders under the age of 5 years.

FUNCTIONING OF THE ACCIDENT AND EMERGENCY DEPARTMENT WITH REGARD TO CHILDREN

Triage

Many accident and emergency departments now use a system of triage to assess and rank patients according to their degree of urgency. This task is performed by experienced nursing sisters or charge nurses and involves assessing the degree of severity of the patient's need and giving first aid treatment such as analgesics or splintage. In some cases investigations such as radiographs can be ordered. In childhood particular note should be made of the fact that 'ambulant' cases, which in adults implies 'not seriously ill', in children refers to the attending adult and not the child. Seriously ill babies can be carried into the accident and emergency department and their parents may wait patiently in a non-urgent queue while the infant's condition becomes worse. All infants should have triage performed immediately they have entered the accident and emergency department.

Play

Play is the means by which young children learn and understand; it distracts them from the distress associated with hospital attendance when ill or injured. Procedures and treatments may be explained to children using the vehicle of play. We recommend that a play specialist is appointed in the accident and emergency department for busy times and that the advice of a play specialist is available to the nursing staff.

Protocols

The wide variety of clinical problems and the urgency with which some present, coupled with the inexperience of junior accident and emergency doctors, makes the use of protocols in accident and emergency of great value. A protocol is not a rigid set of rules but is used to provide structure to thought and action in an emergency situation.[10] Agreed protocols for managing situations such as cardiorespiratory arrest, the multiply injured child, the unconscious child, and the abused child should be drawn up with advice from appropriate specialists.

Records and computerisation

Separate identification of child attenders should be routine in accident and emergency departments. In addition, children of special interest, that is those with medical or social problems, should be easily identifiable. Computerisation of accident and emergency records with additional data on the epidemiology of accidents is of immense use for audit, planning, research, liaison, and accident prevention.

Referral and liaison

The majority of patients attending are managed in the accident and emergency department and its follow up clinics. A substantial minority are referred to other departments for further management. These principally include paediatric medicine, orthopaedics, surgery, burns and plastic surgery, ear, nose, and throat surgery, and neurosurgery. Involvement of anaesthetists is particularly important in the management of patients requiring resuscitation from illness or major injury and in the transfer of severely ill or injured patients to other hospitals. Each department should have medical social workers readily available. Community liaison should be established with doctors in child health, health visitors, and district nurses.

Discharge of patients

When children are discharged from the accident and emergency department ideally their general practitioners should be informed of their attendances and subsequent treatment. In practice, without computerised records, the numbers of attenders are too great to make this feasible. It is useful to give parents written instructions (including those for non-English speaking families) and leaflets should be available for parents' information in, for example: (i) care of wounds, (ii) plaster of Paris, (iii) observations after a head injury, (iv) management of gastroenteritis, (v) the feverish child, and (vi) the convulsing child.

Audit

Many different aspects of audit are relevant in the accident and emergency department. These include efficiency of the service, the appropriateness of clinical care, and referrals to other departments. Internal audit among the staff of the accident and emergency department and audit with other departments in the hospital are of equal value. It is also appropriate for departments in neighbouring districts to hold joint audit meetings.

The role of the paediatrician

The joint statement on children's attendances at accident and emergency departments recommends that all departments should have a consultant paediatrician with responsibility for liaison with the consultant in accident and emergency medicine, concerning the general arrangements for children.[3] This can be achieved in several ways: (i) teaching sessions for accident and emergency staff, (ii) a weekly paediatric clinic in the accident and emergency department, (iii) joint audit meetings, and (iv) agreed protocols.

National liaison

The newly established British Paediatric Accident and Emergency Group (BPAEG) is affiliated to the British Paediatric Association and draws members from paediatrics and from accident and emergency medicine. Links like this and the Royal College of Nursing's Accident and Emergency Forum allow doctors and nurses from different disciplines who are involved in the management of acutely ill or injured children to work together. We propose that consideration should be given to a national committee for children's emergency services. Members could be drawn from paediatrics, accident and emergency medicine and allied specialties, nursing groups, ambulance services, and child accident prevention groups. The remit of such a committee would be similar to that of the Standing Committee on Emergency Medical Services for Children of the American Academy of Pediatrics—that is, responsibility for developing national standards of emergency care for children.

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2 Joint Consultants Committee, chairman Sir John Bruce *Report of a joint working party* London: British Medical Association, 1971
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Persistent proteinuria

The Japanese seem to put an extraordinary amount of effort into screening their children. Not only do they screen for neuroblastoma (see Archivist 1991:1007) but they also test every school child's urine once a year between the ages of 6 and 15. In this way they have found a lot of children with proteinuria. Most of them had transient or intermittent proteinuria, orthostatic proteinuria, or proteinuria associated with haematuria. Between 1976 and 1989, 62 children had renal biopsies performed at Kobe University Hospital because of isolated non-postural proteinuria (1 to 4+ on Albustix) lasting for six months or more. Fifty three had biopsy specimens adequate for examination by light microscopy, immunofluorescence, and electron microscopy and these form the basis of a recent report (Norishige Yoshikawa and colleagues, *Journal of Pediatrics* 1991;**119**:375–9).

Forty two of the 53 children were discovered through the school screening programme. The biopsy specimens of 28 children (group 1) showed 'minimal change' (that is, they were normal or showed slight mesangial proliferation) and those of the remaining 25 (group 2) showed significant pathological changes. These were: focal segmental glomerulosclerosis (FSGS) (n=15), IgA nephropathy (n=4), diffuse mesangial proliferative glomerulonephritis without IgA deposition (n=3), and membranous glomerulonephritis (n=3). Two children with FSGS had had 'minimal change' biopsy appearances two years earlier. There were no clinical pointers at presentation to distinguish those with significant pathology. At follow up for an average of six years seven children (28%) in group 2, all with FSGS, developed chronic renal failure. None in group 1 did so. Three out of 10 children with severe proteinuria and 10 of 43 with mild proteinuria went on to chronic renal failure. Children with persistent proteinuria should be followed up. A renal biopsy will give a better idea about prognosis but otherwise seems unlikely to affect management very much at present.

The routine annual testing of schoolchildren for proteinuria seems to have a greater potential for causing upset than for producing benefit. In Kobe with a population near to that of Scotland such testing detected about three children a year with persistent isolated proteinuria and presumably many more with transient or orthostatic proteinuria. In Finland 11% of nearly 9000 schoolchildren were found to have proteinuria without haematuria but in none was it persistent and none had evidence of significant renal pathology.[1] In America routine urine testing in hospital has been deprecated (see Archivist 1991:266). The national psychology of screening programmes seems a subject worthy of study.

ARCHIVIST

1 Vehaskari VM, Rapola J. Isolated proteinuria.—analysis of a school-age population *J Pediatr* 1982;101:661–8.

CONTROVERSY—REVIEW OF A REPORT

Physical signs of sexual abuse in children

Physical Signs of Sexual Abuse in Children. A Report of the Royal College of Physicians. (Pp 72; £10 paperback.) The Royal College of Physicians of London, 1991. ISBN 1–873240–20–1.

This report comes from a working party set up by the Royal College of Physicians in December 1988, partly in response to the inquiry into child abuse in Cleveland 1987. The college was also concerned over major disagreements between branches of the profession regarding the significance of anogenital signs and the difficulties that were occurring in legal proceedings because of the divergence of views of some medical experts. In relation to this it is worthy of note that neither the British legal nor medical systems impose conditions or criteria on those doctors who set themselves up as medicolegal experts.

The introduction to the book tells us that the members of the working party were invited from all branches of the profession who might reasonably have and interest in the subject. They are not, however, all individuals who will be regularly dealing with cases of child sexual abuse. Those called to give evidence undoubtedly expressed some divergent views and it cannot have been easy for the working party to reach some of their conclusions. It was tempting when reading the report to speculate as to whose evidence was preferred on certain issues.

The terms of reference of the working party were to 'agree terminology, to describe the range of normal findings, to advise on techniques of examination, to produce evidence of what are the physical signs of child sexual abuse, to assess the significance of these in the light of existing knowledge and to produce suitable guidelines for the medical and legal professions and others concerned with sexually abused children'. The report might well have been improved by the inclusion of a legal brain particularly given the frequency with which we are now seeing this book appear in court rooms throughout the country. Indeed, this review was delayed while I retrieved my copy from the Crown Prosecution Service!

Early in the report the authors stressed the need for a consistent vocabulary and promised recommendations for terminology in appendix I. What emerges is disappointing with a glossary of terms for anal abuse only. Furthermore, there are discrepancies between the apparent definitions used in the text and those in the glossary. For example discrepancy in relation to anal fissures makes it difficult to follow the authors' reasoning over the causation and significance of fissures. In the text funnelling is seen as supportive of chronic abuse but in the glossary doubt is expressed over whether the condition exists! It is to be hoped that this portion of the report will be rewritten and a glossary also produced for genital signs.

In the chapter on medical evaluation and technique the working party advocates that a small number of doctors in each district should develop a high skill and experience in dealing with child sexual abuse. While supporting this view there is a need for all those seeing children to know something of the possible ways in which child sexual abuse can present and to be prepared when appropriate to consider it in the differential diagnosis. For example, I was concerned to see that in a recent annotation in this journal on the investigation of rectal bleeding the possibility of child sexual abuse was never mentioned,[1] yet children who have been anally abused often have one or more incidences of bleeding in their history.

I was pleased to see the working party endorsing the view that when a child is brought to see a doctor there is implied consent for any necessary examination.

The committee discourage the use of the prone knee/chest position for examination of the genitalia because of limited experience, seemingly contradicting their view that we need to increase our expertise. I also found myself disagreeing with the reason glass rods were not generally recommended. The working party felt that they should not be used to assess hymenal size because of the dynamic and elastic nature of the hymen. However, one major advantage I have found is that the rods allow demonstration of the potential size of the hymenal opening thereby giving valuable information on the possibility of penetration. In discussing the colposcope, the camera does get a mention; however, the use of photography and methods of recording findings are not discussed in any detail.

It took me sometime to understand why at times I was finding it difficult to follow the committee's reasoning. On a number of occasions they refer to the results in published studies and then pass to their opinion, which the reader is expected to take on trust without knowing the additional evidence upon which their definitive statement is based. Thus a reference to a study in which 22% of girls with a history of penetration (perpetrators' admissions) had no specific signs is followed by the statement that *rarely* findings may be absent even in young girls where both victim and assailant describe penetration. There are several other examples of seemingly non-sequiturs to be found in the report.

A number of papers much quoted in legal proceedings do not get mentioned in the report. An example of this is the paper by Emans *et al* which is often used to support a non-abusive aetiology for attenuation of the hymen.[2] This I do consider deserved further consideration especially as attenuation of the hymen with loss of hymenal tissue is considered by the working party to be diagnostic of penetration trauma by blunt force. When considering foreign bodies the report introduces us to the idea that it is not unusual for a girl to introduce little pieces of toilet paper in to her vagina. This does leave those of us who have never seen a case with a problem!

The longest chapter in the book tackles anal abuse and contains one of the most useful sections of the report which puts the much quoted paper by McCann *et al* into context.[3] As I have indicated above I was left confused by the discussion on fissures in this chapter. Also the report does not tell us how to know the difference between a scar from a healed fissure and the scar of a healed laceration, which it considers to be diagnostic of penetrating trauma. The report appears to rehabilitate reflex anal dilatation as a respectable sign, which if it is greater than 2 cm in the absence of alternative explanations, is more likley than not to be associated with abuse.

Forensic evidence is dealt with in the main body of the report with further useful guidelines in one of the appendixes. Sexually transmitted diseases are dealt with in another appendix but do not include references to the standard venereology textbooks, which still maintain that gonorrhoea can be non-sexually transmitted in children.

The report is a gallant attempt to fulfil ambitious terms of reference but it is not the definitive statement on physical signs that many hoped it would be. There are too many inconsistencies leaving it open to selective quoting in the support of differing points of view. One of the problems may be that the group tried to consider issues in greater depth than did the Committee on Child Abuse and Neglect of the American Academy of Pediatrics.[4] This report should be read for comparison.

It is to be hoped that this report will lead to further discussions and a commitment to reach a consensus on the significance of many physical signs. The manner in which many child protection proceedings are currently vigorously contested is seldom in the best interest of the child and is dreaded by most paediatricians. However, it must be acknowledged that a minority of the medical profession are now dependent on second opinion legal work either as a main source of income or as a way of paying for school fees or skiing holidays.

Furthermore, shortage of resources within health and social services will make it increasingly difficult to undertake rapid and thorough multidisciplinary investigations in cases of suspected child sexual abuse, putting pressure on doctors to provide proof that abuse has or has not occurred. This report can be used to show very clearly that rarely can the doctor be expected to make the diagnosis of child sexual abuse alone.

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LETTERS TO THE EDITOR

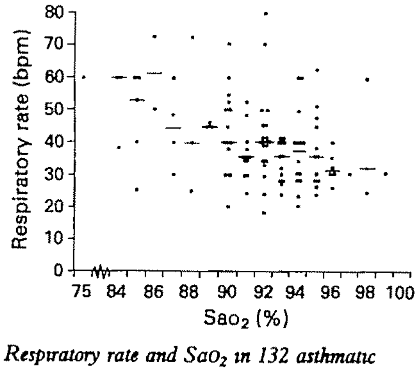
Pulse oximetry in acute asthma

SIR,—I read the article by Bishop and Nolan on pulse oximetry in asthma with interest.[1] Their conclusions about the value of oximetry alone are at odds with the original work of Geelhoed *et al*, who found pretreatment arterial oxygen saturation (Sao_2) highly predictive of outcome,[2] but a number of factors may underlie this discrepancy.

Arterial hypoxaemia, like airway obstruction, is a characteristic feature of acute asthma, reflecting regional abnormalities of ventilation and perfusion.[3] Although oxygen tension is linearly related to forced expiratory volume in one second at all levels of airway obstruction, its relationship to Sao_2 is non-linear and is reflected in the shape of the oxyhaemoglobin dissociation curve. It therefore follows that hypoxaemia accompanying mild airway obstruction may not be detected by pulse oximetry and it is possible that the poor predictive value of oximetry noted by Bishop and Nolan may be attributable to a preponderance of mild/moderate asthmatics in their sample. Unfortunately they do not provide information about selection criteria or other parameters of severity.

Bishop and Nolan noted a correlation of −0·37 between respiratory rate and Sao_2; however, I feel that this may not emphasise adequately the variability in both parameters. For example, in a consecutive series of 132 asthmatic children studied by pulse oximetry at St George's Hospital, London, we noted a wide scatter of pretreatment Sao_2 values. As illustrated in the figure an asthmatic child with a Sao_2 of 90% could have a respiratory rate between 20 and 70 breaths per minute (bpm), and a child with a respiratory rate of 40 bpm could have a Sao_2 anywhere between 84 and 94%. This might suggest that the two variables are measuring different aspects of the acute attack (for example, compensation *v* decompensation) and that both should be recorded.

In our study, as with previous studies, initial Sao_2 neither predicted duration of inpatient stay nor the time spent on nebuliser treatment every two hours. The failure of oximetry to predict outcome may relate in part to the different time courses of recovery for Sao_2 and airway function.[4] In addition clinical decisions after admission are usually made on parameters that reflect airway obstruction such as peak flow measurements and wheezing.



Respiratory rate and Sao_2 in 132 asthmatic children. Bars indicate medians

In general Sao_2 can reflect asthma severity in acute plasma in children, though as with other parameters used in asthma severity scales there is considerable overlap between grades of severity. This should not mitigate against oximetry as a valuable tool in the assessment of asthma in children.

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Drs Bishop and Nolan comment:

Dr O'Keeffe has made an important point about the non-linearity of the relationships of Sao_2 to severity in acute asthma, and the difficulties ensuing when studying predictive accuracy in groups of differing severity. These difficulties apply not only to groups in different settings, but also to comparisons of pretreatment to post-treatment oximetry, and Sao_2 in the very young compared with other children.

Information about selection criteria and severity of patients in our study had been removed from the original paper at the editors request, in order to present a short report. The population of 102 that we studied at the Royal Children's Hospital (RCH) clinic who were included in the oximetry study included 30 referred by a general practitioner and four referred by a specialist, and the remainder referred themselves. Sixteen percent had persistent or frequent episodic asthma, 12% attended with their first recognised asthma ever, and the remainder had a history of infrequent episodic asthma. A total of 43% had a nebuliser at home. The admission rate was a little lower at RCH than that reported in the study of Geelhoed *et al* (42% compared with 54%),[1] though the relapse rate of 46% reported by Geelhoed *et al* means that the unfavourable outcome rate in that study was 75% compared with 52% in our study. Overall it does not seem likely that our study group had a preponderance of mild/moderate asthmatics in the sample, when compared with the group studied by Geelhoed *et al*.

It would not usually be thought necessary to report a scatter plot as illustration of a correlation coefficient, unless the point was to demonstrate outliers or non-linearity. In fact in our data the scatter plot of the relationship of Sao_2 to respiratory rate was similar in appearance to the one Dr O'Keeffe presents (without the corresponding correlation coefficient).

It would, however, be quite incorrect to use a moderate correlation as the basis for inferring that accurate predictions can be made. The evaluation of a diagnostic test is best done using sensitivity and specificity. We would be interested in the values for these parameters for admission from the study that Dr O'Keeffe has carried out.

Recently, Kerem *et al* reported data from which it can be calculated that pretreatment Sao_2 had a sensitivity of 38% for admission (37% for unfavourable outcome).[2] There is not sufficient detail in their report to allow calculation of specificity; however their fig 1 suggests that specificity was very high. Note that in all three studies the specificity of Sao_2 is higher than the sensitivity with one exception: the pretreatment measurement in the study of Geelhoed *et al*.

There is an area of common agreement in the study of Dr O'Keeffe, and studies by Geelhoed *et al*, Kerem *et al*, and our own, namely that oximetry is not accurate enough on its own but is useful as an adjunct to clinical observation. In our paper we attempted to quantify the utility of oximetry when used in combination with clinical judgment, while making use of the best feature of Sao_2, its specificity. This works by using low post-treatment Sao_2 as a criterion for admission, not trusting a high result for Sao_2 as sufficient criterion for discharge, and using highly sensitive clinical criteria as the basis for the decision to admit among those with high post-treatment Sao_2.

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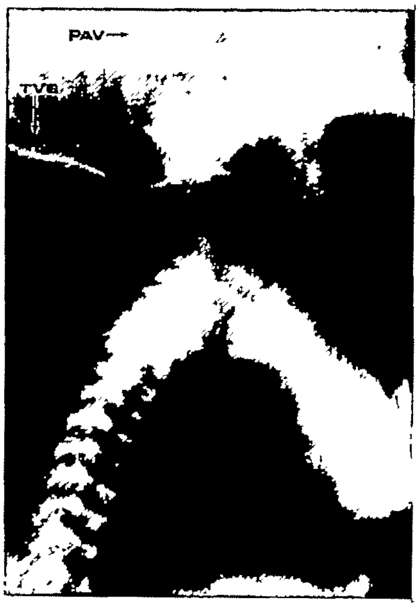
Subdural fat effusion complicating parenteral nutrition

SIR,—I read with interest the report of Rushforth *et al* describing a subdural fat effusion complicating parenteral nutrition but would like to offer a more likely anatomical explanation for this complication.[1]

The venous anatomy of the scalp is very variable and the posterior auricular vein may communicate directly with the intracranial transverse venous sinus via the mastoid emissary vein.[2] The practical significance of this is illustrated by a radiograph of a premature



Radiograph of a premature neonate with venous catheter outlined by contrast material.

neonate who underwent percutaneous insertion of a Vygon central venous catheter after surgery for oesophageal atresia. Injected intravenous contrast material outlines the course of the catheter from posterior auricular vein (PAV) to transverse venous sinus (TVS) via the mastoid emissary vein; contrast also fills the sigmoid venous sinus and internal jugular vein (IJV). Retrograde flow of parenteral feeding solution around a catheter inserted via the posterior auricular vein could therefore reach the transverse venous sinus more directly than the route suggested in the report. Unless the catheter passes directly extracranially to a central vein from this site of entry, which is uncommon, it should be removed. I would endorse previous recommendations that the position of the catheter must always be checked radiographically,[3 4] but would not accept a line inserted via the posterior auricular vein that was 'probably in the external jugular vein'. Optimum catheter tip position is in the mid right atrium but parenteral feeding solutions of restricted osmolality can be safely administered for periods of up to 10 days via catheters positioned directly in central great veins (the superior and inferior vena cavae and the internal jugular vein), provided blood can be freely aspirated through the line.[5]

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Complications of splintage in congenital dislocation of the hip

SIR,—May I comment on the recent report by Langkamer, Clarke, and Witherow?[1] For many years the great majority of infants in Bristol with congenital dislocation of the hip (CDH) have been managed by the neonatal paediatric staff. With a CDH incidence of approximately 1·5% and more than 10 000 births each year, it can be estimated that some 1500 infants will have been treated for a few weeks in a light abduction splint (von Rosen or Aberdeen) during the course of a decade. This form of treatment has proved remarkably effective and safe In a cohort of 445 cases followed up for five years, primary success was achieved in 99% and there were no cases of avascular necrosis.[2] The most serious complications were parental anxiety and superficial skin problems. It was thus with concern that I read of the six infants with splintage complications reported by our orthopaedic colleagues, who further stated that 'these cases illustrate that treatment of neonatal hip instability does have a significant complication rate'.[1] On this basis they then discussed alternative options to early splintage. Unfortunately no information was given in their report on the population from which their cases were drawn. With their help and permission this crucial data can now be made available. The six infants were born between 1980 and 1987; four were referred into Bristol for treatment of their complications, having been born and splinted elsewhere. Of the two Bristol born infants, one was treated by the paediatric staff while the other was referred at once for orthopaedic care because of a second deformity. (It is of interest that four of the six infants had been treated in a Pavlik harness.) Although incomplete, this information appears to confirm the relative safety of early splintage, in sharp contrast to the high morbidity associated with delayed management.[2] All the same I wish to support strongly my orthopaedic colleagues' plea regarding the need for expert supervision and regular review of all abduction splintage

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Children injured by other children

SIR,—At child protection conferences perpetrators of injuries to children cannot always be identified. If parents deny responsibility and have no explanations for the injuries the suspicion is that something is being concealed. There is a grave risk of their children entering the care system because the parents are either believed to be the perpetrators or they are deemed to have failed to protect the children

All workers with children need to be aware of the full range of ways in which injuries occur to children: self injury, injury by parent, by sibling or other children, or by a third party. Some children injure themselves and conceal that they have done so in order to get adults into trouble.[1]

The possibility that one child may injure another, or a sibling injure a sibling, is sometimes too easily dismissed. Research on burned children in the early 1960s showed that nine of 105 children were burned by their siblings or other children—that is, 8·6% of burns in children were child inflicted.[2]

What are the rates of child injured by child for other types of injury that are sometimes unexplained such as bruises, lacerations, fractures, etc?

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Archives of Disease in Childhood 1992, 67: 569–573

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Annotations

Diabetes in puberty

Successful treatment of type I insulin-dependent diabetes (IDDM) is of particular importance during puberty for the achievement of normal growth and sexual maturation and to reduce the risk of long term microvascular complications. Yet, with the onset of puberty, glycaemic control as judged by serial glycated haemoglobin (HbA_1) concentrations, may deteriorate.[1–3] This deterioration is often attributed to the psychological problems of adolescence and poor compliance with diet and insulin dosage.[4 5] However, over the last few years it has become clear that this is not the complete explanation and that the endocrine changes of puberty may also contribute to the poor glycaemic control, disordered growth and sexual maturation in IDDM.

Insulin resistance during puberty

Normal pubertal development is associated with dramatic changes in insulin sensitivity and fasting insulin concentrations rise during puberty reaching a peak in both sexes at stage 3 and 4 before declining and returning to prepubertal values during early adult life.[6] Furthermore, during puberty the plasma insulin responses to both oral and intravenous glucose are greater than those observed in younger children or adults.[7 8] Using the hyperinsulinaemic clamp technique Amiel *et al* [9] showed an appreciable reduction in insulin stimulated glucose metabolism in pubertal compared with prepubertal and adult subjects which resulted from decreased glucose uptake in muscle rather than any change in hepatic glucose production rates.[10] Similar changes of insulin sensitivity can be demonstrated in adolescents with IDDM. As in normal subjects, insulin resistance is maximal in late puberty but at every stage of puberty diabetics are more insulin resistant than controls.

Growth hormone

In their studies, Amiel *et al* demonstrated a correlation between changes in insulin sensitivity and mean growth hormone concentrations.[9] Puberty is characterised by an increase in growth hormone pulse amplitude,[11] and mean overnight growth hormone concentrations rise during puberty being maximal in mid to late puberty corresponding to the changes in insulin sensitivity.[12] Some authors have noted an earlier rise in growth hormone concentrations in girls[13] corresponding to the earlier pubertal growth spurt whereas sex differences in the timing of changes in insulin sensitivity have not been consistently demonstrated.[14 15]

In adolescents with IDDM, plasma growth hormone profiles are characterised by an increase in both pulse amplitude and baseline concentrations.[13] Growth hormone excess has been shown to impair the ability of insulin to suppress hepatic glucose production and to stimulate peripheral glucose uptake.[16 17] Direct evidence that these high growth hormone concentrations are responsible for the increased insulin resistance during puberty in IDDM has largely been gathered from studies of the dawn phenomenon. In subjects with IDDM insulin requirements increase overnight and are maximal between 8.00–9.00 am. The extent of this overnight change in insulin sensitivity can be correlated with mean growth hormone concentrations and it is reversed after suppression of growth hormone secretion.[18 19] The dawn phenomenon is maximal at puberty stage 3–4 in both sexes,[18] but there is considerable variation between and within individuals which leads to major problems targeting insulin treatment during puberty.

Failure of current insulin regimens

Although it has long been recognised that insulin requirements in IDDM rise during puberty, increases of insulin doses of up to 1·5 units/kg/day only lead to marginal improvements in HbA_1 concentrations.[20] It could be argued that greater increases are necessary but current insulin regimens do not permit appropriate insulin delivery overnight.[21] Even where the long acting insulin is given late at night as part of a multiple injection treatment, free insulin concentrations tend to be high during the early part of the night and then wane as the night proceeds. The over insulinisation during the early part of the night can lead to a high incidence of unrecognised hypoglycaemia,[22] and the low concentrations of insulin during the latter part of the night often fail to control the dawn rise in blood glucose concentrations.

The failure to achieve appropriate insulin concentrations overnight may also lead to an increase in growth hormone secretion. Hyperinsulinaemia during the early part of the night may stimulate growth hormone secretion directly[23] or as part of a counter-regulatory response to hypoglycaemia.[24] Low concentrations of insulin during the latter part of the night lead to a decrease in insulin-like growth factor I (IGF-I) bioactivity with a resulting feedback drive for further growth hormone secretion. The role of insulin in the regulation of the growth hormone/IGF-I axis in IDDM has only recently been elaborated. Despite high growth hormone concentrations, serum concentrations of IGF-I tend to be low in IDDM. This growth hormone resistance may be the result of inadequate portal delivery of insulin as insulin has a permissive role in growth hormone receptor function. The major IGF-I binding proteins (IGFBP-3, IGFBP-1) are also altered in IDDM.[25] IGFBP-1 appears to be an inhibitor of IGF-I bioactivity and its concentrations are reciprocally regulated by insulin.[26] Inadequate insulin concentrations overnight lead to a rise in IGFBP-1 and a fall in IGF-I bioactivity: the degree of abnormality in IGFBP-1 can be directly correlated with HbA_1 values.[25 27]

Increasing insulin doses to achieve concentrations necessary for suppression of IGFBP-1 may only lead to unacceptable hypoglycaemia without necessarily suppressing growth hormone secretion During puberty the very high growth hormone concentrations may also lead to accelerated ketogenesis and contribute to the rapid decompensation and diabetic ketoacidosis which result from poor compliance.

Growth and pubertal development

Low circulating IGF-I concentrations and reduced bioactivity in IDDM could lead to abnormalities of pubertal growth. Severe abnormalities are now infrequent but the pubertal growth spurt may be blunted particularly in girls.[28] In early studies, sexual maturation was also delayed in many children with IDDM, but this is now rare although a dissociation between pubarche and adrenarche has been reported.[29] Menstrual irregularities appear to be more common in adolescents with IDDM and may be related to low concentrations of sex hormone binding globulin.[30]

Growth problems are often more severe in adolescent girls with IDDM and other sex differences can be demonstrated. Glycaemic control as judged by HbA_1 is often worse in boys during early puberty and in girls during later puberty.[1] The tendency to put on excessive weight is also more common in late adolescent girls and cannot entirely be explained by disordered eating habits and differences in exercise patterns.[31] Further studies of the endocrinology of puberty are needed to explain these sex differences and to understand the well documented effects of puberty on the rate of development of diabetic microangiopathic complications.

Conclusions

Pubertal development is accompanied by rapid growth and an almost doubling of lean body mass. The provision of adequate nutrition and appropriate insulin requirements in adolescents with IDDM is therefore a major challenge. The insulin dose should be increased, either in line with pubertal development or growth,[32] and requirements may reach 1·5–2·0 units/kg/day. It is important, however, to be aware of the risks of over insulinisation overnight and it must be remembered that insulin requirements fall back to prepubertal concentrations at the end of the teenage years. Failure to reduce insulin requirements in the late adolescent girls may aggravate weight gain.

Multiple injection treatment not only offers greater advantages for the adolescent but also provides a logical way of delivering basal insulin requirements during puberty. However, treatment with pen injectors will not necessarily improve glycaemic control and overnight insulin profiles may be far from satisfactory.[21] Continuous subcutaneous insulin delivery has not proved acceptable in adolescents with IDDM and the development by the pharmaceutical industry of more stable long acting insulins should be encouraged. Finally direct attempts to reduce growth hormone secretion without compromising growth might have a place in the treatment of the adolescent with IDDM. Poor compliance during adolescence should not be unexpected, given the rigours of the diabetic regimen. It is therefore important that good compliance is rewarded by an improvement in glycaemic control, normal growth and development and a reduction in the risks of diabetic complications.

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'Personal child health records' held by parents

'By comparison with the situation 50 or 100 years ago, women are well educated; they are able to acquire and weigh up knowledge and advice from a wide variety of sources, including friends and relatives, books and magazines. They are highly motivated and will seek help if and when they need it from health staff, and are also willing to use services if requested to do so'.[1]

The idea is a simple one—that the medical records of a child are primarily to aid the exchange of information between professionals whenever they undertake to help care for a child. The parents are the professionals who carry out most of the health and illness care of an individual child and to aid them in this they need to have full and immediate access to all the relative information.

Are medical records primarily to aid in the exchange of information between professionals?

There are of course many reasons for keeping records—legal, epidemiological, research, etc—but these are, and should remain, secondary to meeting the need to share information so as to provide optimal health and illness care to an individual. This optimal care will, *very occasionally,* include health care professionals withholding information from one another and in doing so they have to undertake the responsibilities that arise from such an action. Parents certainly, under some conditions, may withhold information about a child from the medical professionals, and on occasions the reverse will also be true. In both cases the carer may have the child's best interest at heart, or, although they may not realise or admit it, their own best interests at heart. Examples of the latter are easy to find: the parent may not want to reveal worries about child abuse because they think it is being carried out by their spouse, and a doctor may not want to reveal her worry about a child being abused to the parent because of the furious reaction that this may engender.

However to aid information exchange, secondary considerations need to be considered second.

Who are the health professionals who look after the health and illness care of children?

Children are primarily looked after on a 24 hour a day, seven days a week, 365 days a year basis by their parents (yes, there are exceptions, but they are exceptions). The evidence is that most parents are devoted to maintaining the health of their children.[2] Hardly surprising as the continuation of the human race depends on it.

Giving parent's diaries to keep about how they deal with their children's illness shows that in most cases these are managed by parents without referring to a medical professional.[2 3] However children's health and their illnesses are in the minority of cases also coped with by relatives, childminders, teachers, nurses, doctors, playgroup leaders, next door neighbours, etc. All these people may be aided in doing this by access to the relative medical information.

Where do health professionals deal with health and illness in children?

The majority of health and illness in children is looked after by the parents at home. However there are a large number of other places that the child may be cared for: including at the childminder, playgroup, nursery, school, doctor's surgery, child health clinic, a hospital accident and emergency department, hospital inpatients' and outpatients' departments, etc. Access to records are needed in all these places.

How are these needs for access to information about a child best met?

The needs can be met by a 'personal child health record' held by the parents. Available research shows that (i) parents want to hold their own record[4]; (ii) do not loose the record significantly more than the medical system does[5]; (iii) general practitioners and health visitors like the system; (iv) that the system is particularly valuable with mobile families such as service and travelling families[6]; and (v) that parent held records are filled in better than clinic held records.[5]

What does the 'national' record consist of?

It is A5 horizontal size and has a bright red plastic cover (all the easier to find it with) with two clear plastic pockets in the inside. There are 50 loose leafed punched sheets fastened in the record using a white soft plastic covered metal rod so that pages can be easily added (or taken out). The details on these pages include information about the child's address, doctor, health visitor, major health problems, family history, birth details, clinic/home visits, immunisations, growth charts, routine reviews, all consultations, and a help section including teeth care, feeding advice.

There are pages of questions for parents to fill in about their own health and about their own observations of their child's health and development. There are also 'injury prevention' messages throughout the record at development appropriate intervals to be discussed between the primary health care team and the parents.

What have been some of the main problems encountered since launching a national record?

One of the main problems was agreement over the overall contents of the record. A national version was agreed upon and the details published in a report by the original working party made up of representatives from the Royal College of General Practitioners, the British Paediatric Association, the British Medical Association, and the Health Visitors Association.[7] The working party accepted that there would always be argument over the contents. However the record recommended is loose leafed and can be adapted to the needs of local service providers and individual children. The contents are under constant revision and the reconvened national working party will be reporting on the new recommended version in the middle of 1992.

Then there is the issue concerning who actually 'owns' the record. The legal, medical, and ethical issues that surround this question are complex and still under discussion with the Department of Health. Meanwhile some districts categorically state that the record belongs to the parents, others to the state, others to the local district health authority.

Also who should pay for the record? The Department of Health, although fully supporting the concept of personal child health records held by parents, has stated that it does not see itself responsible for financing the record. This has been left up to the ingenuity of local districts. Getting the parents, the district, the family health services authority, or drug companies to pay—have all been looked at and variously used.

Linking the information in the record to various computer systems is a problem because there is not a single standard computer system in all districts. Luckily most districts use the National Child Health Computer System, but others do use alternatives. The design of certain of the pages concerned with the routine checks on the child and the immunisations done have been made similar to the 'screens' on the national computer system, with non-carbonated copies of these pages being sent centrally for the information to be put onto the district health authority computer system. Problems arise however as this compromises the records' 'user friendliness' for parents.

There is the question as to whether there is a need to keep parallel records. General practitioners are legally bound to keep there own standard practice records on their own patients. What records other professionals have to keep (health visitors, community doctors, therapists, etc) depends on the needs of individual practitioners in their care of the individual children. Where there is a question of possible or actual child abuse it is recommended that parellel records should automatically be kept, but that the parents should be informed of this.

What of the future?

With recent recommendations from the Department of Health and the Foundation for the Study of Infant Deaths consideration will now be given to having a page/pages devoted to the prevention of sudden infant death syndrome, including information concerning the position a child is put down to sleep and the hazards of smoking. Sometime in the future, after further research, consideration may also be given to having a modified system of aiding parents to recognise significant signs and symptoms of illness in their children.

Pages for the record concerning the health and development of school age children are under consideration. There are, however, a number of problems. First is the whole question of the future provision of school health services. Second is the fact that sometime during the school age years, the focus of responsibility for health shifts from the parents to the child. Third is the lack of available research showing the value of detailed health promotion in this age group. All this also raises the issue as to when the record should be given to a young adult, and for the more distant future, whether the record could continue to be used on into adult life.

A further proposition for the future is to keep a national 'library' of different pages for the record as developed by different people in different districts. The need for such a library containing all the variations on the national record has become obvious, but who should keep it and how it should be financed has yet to be settled.

There is also the need for further research to look at the costs, benefits, and drawbacks to further developments in the record. For instance new national centile charts are being drawn up in the light of the evidence that the present Tanner and Whitehouse charts are outdated. These new charts will be completely redesigned using information available from the various present databases concerned with the growth of children.

In conclusion, the development of a national personal child health record far from being a 'one off' concept is an ongoing dynamic entity that consumes much time and work, but also offers great rewards as long as it is recognised that the ideal should not stand in the way of putting into practice what is merely a great deal better than what was there before. How well it works does not only depend on its use by parents but even more so on its use by, and the value attached to it by, doctors and nurses both in the community and hospital, If it is valued by them, then the parents will value it too, will not loose it, and will bring it with them to all contacts with the primary and secondary care providers to share the information so as to ensure the better care of their child.

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Medulloblastoma

The treatment of childhood brain tumour is a subject that represents a major challenge and yet remains a major frustration to the paediatric oncologist. Medulloblastoma is a rare, highly malignant tumour usually arising in the vermis of the cerebellum. It accounts for approximately 30% of childhood brain tumours, or one child per 150 000 per year (80 cases year in the UK). The tumour can occur at any age through childhood with a peak occurring around the age of 5 years. Males are slightly more often affected than females. Medulloblastoma is therefore a rare diagnosis in the majority of paediatric units and is a tumour of sufficient rarity that international cooperation has been essential to study possible treatment advances.

The histological origin of the medulloblastoma is uncertain. It may arise from embryonal rest cells left behind after the development and subsequent disappearance of the outer granular layer of the cerebellum in the roof of the fourth ventricle An alternative theory is that medulloblastoma originates from undifferentiated cells in the subependymal region in the roof of the fourth ventricle. These cells have the ability to differentiate into neuronal and glial cells and are found in all ages and in various areas of the brain, in particular in the area of the fourth ventricle, in the cerebellum, and in those parts of the pallidum, nucleus caudatum, and thalamus that are next to the ventricles. Medulloblastoma-like tumours arise in these areas and this observation has led Rorke to suggest that the term 'primitive neuroectodermal tumour' (PNET) should be applied to all of these tumours.[1] Other pathologists however disagree with this view and suggest that the term medulloblastoma should be reserved for tumours arising in the classical site, that is the cerebellum, and the term PNET be used for similar tumours arising elsewhere in the central nervous system.

Diagnosis is usually made by computed tomography after clinical suspicion of raised intracranial pressure. There is however no 'classical' appearance of medulloblastoma on a computed tomogram and the diagnosis must be histologically confirmed.[2] The relief of raised intracranial pressure is a surgical emergency and is best achieved by removal of the tumour rather than by ventriculoperitoneal shunting, although this may at times be necessary. Once raised intracranial pressure is relieved it is essential to obtain imaging of the spine either by a computed tomographic myelogram or by a gadolinium enhanced magnetic resonance image. As many as 20% of childhood medulloblastomas have clinically unsuspected spinal deposits present at diagnosis.[3] If present these require treatment with enhanced spinal radiotherapy doses and are an indicator of poor ultimate outcome.

Surgery alone is a never curative treatment for medulloblastoma and postoperative radiotherapy is essential. The tumour originates in contact with the cerebrospinal fluid and this is the pathway of metastatic spread. Radiotherapy therefore is needed to treat the tumour bearing area and also to treat 'prophylactically' the rest of the cranium and spine. Disease free survival is related to the dose of radiotherapy. The minimum dose to the tumour bearing area should be 55 Gy and the craniospinal dose 35 Gy. Unfortunately these doses when delivered to the developing brain will often be accompanied by long term sequelae. Growth failure is common and is due to a combination of failure of spinal growth and growth hormone deficiency. Many studies have shown that there is loss of intellectual function which becomes more severe the younger the child is at the time of treatment.[4]

At the present time 60% of children with medulloblastoma can expect to be long term survivors when treated with maximal surgical removal of their tumour followed by radiotherapy. Current clinical research is therefore concentrated on two questions: (1) can this figure be improved upon and (2) can treatments with fewer long term sequelae be devised?

Chemotherapy has and is being studied in the context of international randomised clinical trials. Many chemotherapeutic agents have been shown to be effective in producing remissions in children with either recurrent medulloblastoma or in children with measurable residual disease after surgery and radiotherapy. The first randomised studies carried out in Europe and the USA showed that there appeared to be a marginal benefit when chemotherapy with vincristine and lomustine (CCNU, Lundbeck) was given after radiotherapy.[5] [6] The second generation of studies sought to exploit the time period between surgery and radiotherapy, which is a theoretically advantageous window of time in which to give chemotherapy. This has failed to show any advantage using the drugs and doses prescribed in the second European trial.[7] Results of the similar American trial are awaited. The European and American studies sought to improve quality of survival by reducing the prophylactic craniospinal radiotherapy for children who appeared to have had complete surgical removal of the primary tumour and no demonstrable metastatic disease. Both studies have shown that this had a deleterious effect on survival and this approach has therefore been abandoned.

New studies about to be launched in Europe have been developed by the UK Children's Cancer Study Group and the International Society for Paediatric Oncology. For children over the age of 3 years intensive chemotherapy using carboplatin, cyclophosphamide, etoposide, and vincristine given after surgery and before radiotherapy will be compared with classical radiotherapy alone. For children under 3 years an intensive chemotherapeutic schedule lasting one year will be studied. Radiotherapy will be withheld during this time thus allowing time for the completion of development of the central nervous system. Once the child is beyond the third birthday, radiotherapy will be given to the tumour bearing area only, thus hopefully improving survival and quality of survival.

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Archives of Disease in Childhood 1992, 67: 574–579

ORIGINAL ARTICLES

Profile of bronchial responsiveness in children with respiratory symptoms

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Accepted 11 December 1991

Abstract

A postal questionnaire inquiring into the presence of respiratory symptoms was sent to 3698 children aged 7 and 8 years. Those reporting either cough or wheeze were randomised, and a sample invited to attend for skin testing. A total of 192 symptomatic children, half of whom were atopic and half non-atopic, were randomly selected to enter the study.

All children performed and recorded best of three peak expiratory flow measurements twice a day and completed a 10 point respiratory symptom score card each day for one year. They also recorded all treatment taken and made a note of relevant life events.

Each child was seen monthly for general assessment and for measurement of non-specific bronchial responsiveness to methacholine. Of the 192 children, 183 successfully completed the study. For six subjects 11 measurements of the provocation dose required to cause a 20% fall in forced expiratory volume in one second (PD_{20}) were available for analysis and on the remaining 177, ≥12 measurements.

The prevalence and degree of bronchial hyper-responsiveness (PD_{20} $<6\cdot4$ μmol) and its relationship to atopy was examined by comparing the percentage of members of each symptom group demonstrating bronchial hyper-responsiveness and the number of occasions on which they did so, and by comparison of minimum and median PD_{20} values. The range of bronchial responsiveness shown during the study period by each child was expressed as doubling doses of methacholine and compared between symptom groups.

Atopy and wheeze were both independently associated with an increased prevalence and greater degree of bronchial hyper-responsiveness when compared with non-atopy and cough respectively, all differences being significant at the 0·001 level. Thirty three per cent of subjects demonstrated a range of methacholine responsiveness of >4 and 13·4% of >6 doubling doses during one year.

Respiratory symptoms are common in childhood with as many as 25% of children aged 7–10 years being troubled by recurrent episodes of cough and wheeze.[1] However, a diagnosis of asthma is made in less than half this number,[2] despite the recent appreciation of asthma as a range of diseases with differing clinical manifestations. This under diagnosis leads to under treatment and increased respiratory morbidity.

Many, but by no means all, asthmatic subjects demonstrate bronchial hyper-responsiveness (BHR),[3] as do a proportion of adult subjects suffering from respiratory symptoms in the absence of diagnosed asthma.[4] However, because of its lack of specificity and low sensitivity for asthma, non-specific bronchial challenge has not proved to be a diagnostic test as was once hoped.[5–8] Measurements of bronchial responsiveness may, however, serve as a useful laboratory tool, and as BHR may be potentially of importance in the pathogenesis of chronic obstructive pulmonary disease in adult life,[9] this phenomenon merits the fullest investigation.

Much of the current knowledge regarding the relationship between bronchial responsiveness and other factors such as symptoms, measurements of airflow obstruction, and atopic status has been derived from studies that were cross sectional in nature, and assumptions often made on the basis of single measurements of reactivity. Whereas the short term repeatability of bronchial challenge testing is good,[10–12] less is known about its longer term stability, but what evidence there is suggests that levels of bronchial responsiveness can vary appreciably with time and life events.[13]

In adult life there are several pulmonary pathologies that may produce overlapping symptom complexes. Thus when studying adult populations researchers are often tempted to choose highly polarised groups of mild stable asthmatic and strictly normal subjects for investigation.[14] However, the study of these homogeneous groups can make it difficult to examine the determinants of airways responsiveness, and such studies may produce results which, when extrapolated to the population at large, are at odds with the findings of large, epidemiological surveys. In their work published in 1990, Pattemore *et al* highlighted the need for longitudinal studies which can assess the time related determinants and patterns of change of bronchial responsiveness.[15]

Our aim was to examine over one year a large, heterogeneous, randomly selected group of children with respiratory symptoms but not necessarily a diagnosis of asthma in order to examine both the prevalence and the severity of bronchial responsiveness and its relationship to atopy.

This work formed part of a community based longitudinal study, further details of which are reported elsewhere.[16]

Subjects and methods

SELECTION OF SUBJECTS

A postal questionnaire inquiring into the presence of respiratory symptoms in the past 12 months was sent to the parents of all children born between 1 July 1978 and 30 June 1980 registered on the practice lists of 86 primary care physicians working in five large local health centres. These numbered 3698. The questionnaire was a brief and simple document that used three questions from a larger questionnaire described and tested for repeatability by Clifford *et al.*[1] The relevant questions were: (1) Has your child had an attack of wheezing at any time during the last 12 months? (2) In the last 12 months, has your child seemed to cough more (or to get more coughs) than other children? (3) In the last 12 months, has your child woken at night with coughing for 3 or more nights in a row (apart from during the first 5 days of a cold)?

The positive responders were identified. For a child to be designated as having cough, it was necessary for them to have answered in the affirmative to one or both of the cough questions, but to have answered in the *negative* to that on wheeze. For a child to be designated as having wheeze, they must have given a positive reply to the wheeze question, and may have answered in the affirmative or the negative to the cough questions.

A random sample of children from each symptom group were tested by skin prick to three allergens: *Dermatophagoides pteronyssinus*, cat dander, and mixed grass pollen to ascertain their atopic status. The following four groups, each consisting of 48 children willing to enter a one year longitudinal study, were recruited: (i) atopic children with wheeze, (ii) atopic children with cough, (iii) non-atopic children with wheeze, and (iv) non-atopic children with cough. Further details of the selection and skin testing of subjects has been reported elsewhere.[16]

Table 1 Calibration of DeVilbiss nebulisers: variability and mean outputs

Nebuliser No	*Mean output (ml)*	*SD*	*Coefficient of variation*	*% Mean difference*
1				
Day 1	0·00234	$1{\cdot}21\times10^{-4}$	5·17	11·6
Day 2	0·00265	$1{\cdot}40\times10^{-4}$	5 27	
2				
Day 1	0·00235	$3\ 84\times10^{-4}$	16·5	8·5
Day 2	0·00257	$1{\cdot}71\times10^{-4}$	6·6	
3				
Day 1	0·00256	$2{\cdot}35\times10^{-4}$	9·17	10·1
Day 2	0·00285	$1{\cdot}56\times10^{-4}$	5·43	
4				
Day 1	0·00238	$1{\cdot}84\times10^{-4}$	7·73	0·8
Day 2	0·00240	$7{\cdot}60\times10^{-4}$	3·16	
5				
Day 1	0·00255	$1{\cdot}44\times10^{-4}$	5·64	8·6
Day 2	0·00233	$1{\cdot}23\times10^{-4}$	5·27	
6				
Day 1	0·00222	$2{\cdot}87\times10^{-4}$	12·9	5·4
Day 2	0·00210	$5{\cdot}82\times10^{-5}$	2·77	
7				
Day 1	0·00188	$1{\cdot}60\times10^{-4}$	8 55	2·6
Day 2	0·00192	$1{\cdot}22\times10^{-4}$	6·35	
8				
Day 1	0·00175	$1{\cdot}05\times10^{-4}$	6·00	3 8
Day 2	0·00182	$2{\cdot}42\times10^{-4}$	13·2	

Permission to carry out this study was granted by the Southampton University and Hospitals ethical subcommittee and written parental consent obtained for all stages of the study.

METHODS

The one year longitudinal study commenced in November 1987. At the start of the study each child was issued with a peak flow meter (Vitalograph) and instructed in its use. The children were asked to perform three peak expiratory flow (PEF) manoeuvres each morning and evening and to record the highest of the three readings. They also completed a symptom score card each day which inquired into 10 different upper and lower respiratory tract symptoms. On this card they also recorded all medications taken and made a note of relevant life events.

The children attended special clinics every four weeks for general assessment and for methacholine bronchial challenge. At the first visit each child's height was recorded and predicted values of forced expiratory volume in one second (FEV_1) and PEF based on height were calculated. A current drug history was taken, and children were asked not to use inhaled β_2 adrenoceptor agonist for six hours before each visit. All other antiasthma medication was withheld for 12 hours.

Methacholine challenge was performed using the method described by Yan *et al.*[10] The method was modified in the following ways: a set of four nebulisers with known and consistent outputs was selected for each of the two investigators who performed the challenge testing as follows. Each investigator assessed the outputs of 10 nebulisers by weighing them before and after 10 activations, the initial content being 1 ml of 0·9% sodium chloride. This procedure was repeated nine times. Variability in the output of the nebulisers was determined by the analysis of variance, in order to derive both the within-day and between-day coefficients of variation for each nebuliser. The eight nebulisers with the smallest coefficients of variation were subsequently used in the challenges. The within-day and between-day coefficients of variation for these nebulisers are shown in table 1.

Solutions of methacholine, prepared in 0·9% sodium chloride, were made up for each nebuliser taking into account the mean output of each instrument such that the first delivered exactly 0·025 μmol, the second 0·1 μmol, the third 0·4 μmol, and the fourth 0·8 μmol per puff. A fifth nebuliser was used to administer saline.

At the start of each visit, baseline FEV_1 manoeuvres were performed to obtain two technically acceptable recordings within 100 ml. If the higher of these exceeded 60% of the predicted value for the child's height and age the challenge proceeded. The children were instructed in the use of the nebulisers. Once the investigator was satisfied that the child could perform the procedure correctly, two puffs of 0·9% sodium chloride were administered.

Provided the subject's FEV$_1$ did not fall by >10% of baseline value, the procedure was repeated using incremental doses of methacholine from 0·025 µmol to 6·4 µmol until either the FEV$_1$ fell by greater than 20% of baseline or the final dose was reached. On completing the challenge, 100 µg of salbutamol was administered where appropriate by inhalation from a spacer device in order to restore airway calibre to basal levels.

If the initial baseline measurement of FEV$_1$ was <60% of predicted, then a reversibility test using 100 µg of salbutamol inhaled from a spacer device was performed, with readings of FEV$_1$ being made at five and 10 minutes after inhalation. Throughout the course of the study, all challenge testing was performed by two testers, each child being tested by the same tester on >90% of occasions. A qualified physician was present at all times.

The repeatability of the challenge procedure was ascertained on a random subgroup of children. These children underwent methacholine bronchial challenge on two consecutive days, the tests being performed by the same investigator, at the same time of day.

DATA ANALYSES

All data were transferred to the University of Southampton mainframe computer, and were then checked against the original data source. All data were entered twice, and checked for accuracy. The Statistical Package for Social Sciences was used in the analyses.

In order to study the temporal relationship between the provocation dose required to cause a 20% fall in FEV$_1$ (PD$_{20}$), PEF, and symptoms, the data for each of the 192 subjects commencing the study were plotted graphically. An example is shown in fig 1. Though the information gained from examination of these charts was necessarily subjective, it proved invaluable in directing further analysis, as manipulation of the data was difficult owing to its size (>800 000 data points).

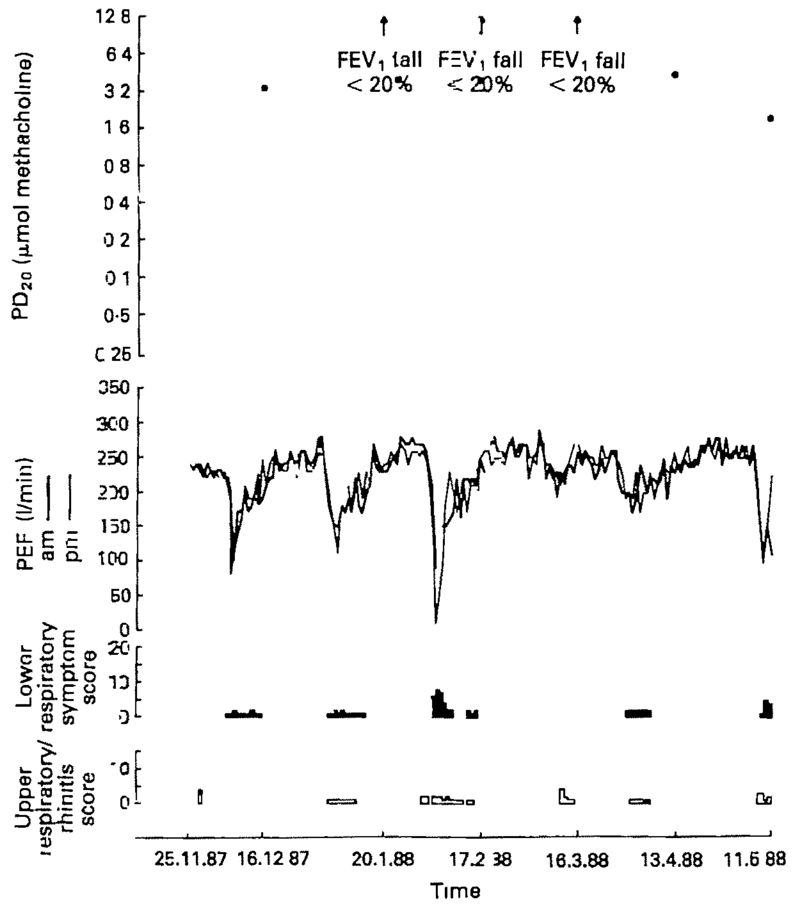

Figure 1 Graphical representation of data, collected over a period of six months, from a 7 year old atopic child with cough, showing respiratory tract symptoms and falls in PEF occurring in parallel, not accompanied by changes in methacholine responsiveness.

Calculation of PD$_{20}$ values

For each challenge the fall in FEV$_1$, expressed as a percentage of the highest value after saline, was plotted against the cumulative dose of methacholine on a logarithmic scale. The PD$_{20}$ was estimated by log linear interpolation from the dose response curve. BHR was defined as a PD$_{20}$ value of <6·4 µmol methacholine, in keeping with other studies of methacholine bronchial responsiveness.[1 13] Values of PD$_{20}$ beyond this point were regarded as being indeterminable. For each child the first methacholine challenge of the year was regarded as a teaching exercise and the result not used in the analyses. The subsequent 11 (n=6) or ≥12 (n=177) measurements for each subject were analysed.

For each of the four symptom groups, the following parameters were calculated: (1) The percentage of the subjects in the group who, at any time during the year, demonstrated BHR. (2) The median number of times (maximum 12) the subjects in the group were hyper-responsive. (3) The minimum PD$_{20}$ (by calculating the group median of the lowest recorded PD$_{20}$ values for each subject). (4) The median PD$_{20}$ (by calculating the group median of the median value of 12 PD$_{20}$ values for each subject). Kruskal-Wallis test was used on data from the four groups of subjects to establish the existence of a difference, and then Mann-Whitney U test was applied to combined data as shown in table 2 in order to assess the significance of that difference.

The range of bronchial responsiveness to methacholine during the study period was calculated for each child, expressed as doubling doses of methacholine, and the number of children demonstrating ranges of PD$_{20}$ >4, >5, and >6 doubling doses calculated. All subjects were included in this analysis, although many of them did not demonstrate BHR on some or all occasions of testing, and only PD$_{20}$ values <6·4 µmol could be analysed.

Repeatability of the methacholine challenge test for a subgroup challenged on two consecutive days was expressed as the difference in relation to the mean for each of the pairs of values (coefficient of repeatability).[13]

Results

Altogether 183 of 192 subjects completed the 12 month long study, and of the nine who did not, three had performed 12 or more challenge procedures and were included in some analyses.

Table 2 Percentage in each group ever demonstrating BHR, median number of occasions subjects demonstrated BHR, and group minimum and median PD_{20}

Group	*% ever demonstrating BHR*	*Median No occasions BHR demonstrated*	*Minimum PD_{20} (μmol methacholine)*	*Median PD_{20} (μmol methacholine)*
Atopic+wheeze	89 0	11	0 40	1 43
Atopic+cough	35 7	5	1·26	>6 4
Non-atopic+wheeze	30 8	4	1 29	>6 4
Non-atopic+cough	7 7	1	5 50	>6 4
Atopic	57 1*	8*	0 82*	5 14*
Non-atopic	14·3	2	2 85	>6 4
Wheeze	61·5*	8*	0·64*	5 04*
Cough	14 3	2	2·85	>6 4

*Mann-Whitney U test, p<0 001

After exclusion of the first test, each child was subjected to 11–15 (median 13) methacholine challenges. Using the analysis of Bland and Altman, the coefficient of repeatability, calculated on data from the 14 children who performed methacholine challenge on two consecutive days, was 1·3 doubling doses (table 3).

The prevalence of BHR in each symptom group is shown in table 2. Prevalence figures are also given for all atopic subjects and non-atopic subjects, and for those with wheeze and cough collectively. BHR was positively associated with both atopy and wheeze (Mann-Whitney U test, p<0·001), and no interaction between these factors was demonstrated. Despite significant symptoms, only 7·7% of the non-atopic subjects with cough demonstrated BHR on one or more occasions during the study period.

Table 3 Results of repeat methacholine challenge on two consecutive days in a subgroup of 14 children with BHR

Subject No	*Day 1*		*Day 2*	
	PD_{20} (μmol methacholine)	*lg_2 PD_{20}*	*PD_{20} (μmol methacholine)*	*lg_2 PD_{20}*
1	1·020	0·028	2·330	1 220
2	0·990	−0 014	0 870	−0·200
3	1·041	0 057	0·624	−0 680
4	4·622	2·205	2·848	1 508
5	1 566	0·637	1·490	0 578
6	1·492	0 578	1 660	0·734
7	2·400	1·262	1 896	0 923
8	2·706	1 435	3·400	1 766
9	0 033	−4 913	0·027	−5 235
10	1·462	0·548	2·251	1 170
11	0·351	−1·505	0 180	−2·471
12	0·202	−2 305	0·118	−3·073
13	3·994	1 996	5 444	2·441
14	0 172	−2·538	0 210	−2 249

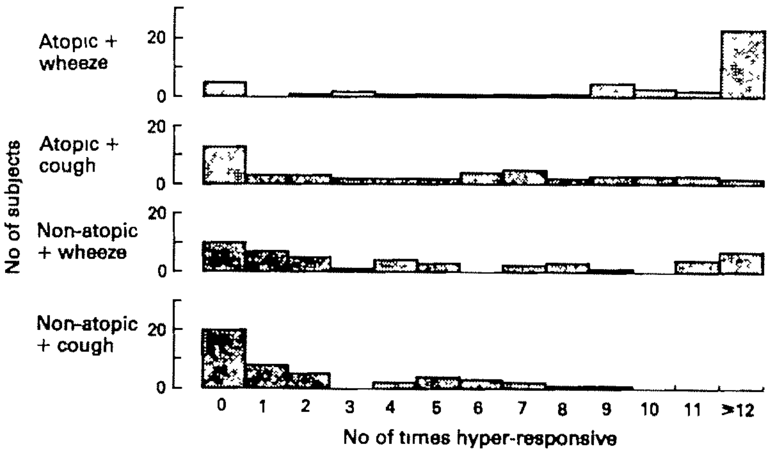

Figure 2 Frequency distribution of the number of times (maximum 12) that subjects in each of the four symptom groups demonstrated bronchial hyper-responsiveness to methacholine.

Figure 2 represents, for each symptom atopy group, the frequency distribution of the number of occasions each child exhibited hyper-responsiveness to methacholine. The median number of occasions on which each subject demonstrated BHR during the year was calculated, and the median for each group is shown in table 2. Subjects with atopy and those with wheeze demonstrated BHR on significantly more occasions when compared with those who were non-atopic and those with cough respectively (Mann-Whitney U test, p<0·001). No interaction was demonstrated between atopy and wheeze. The frequency distribution of median PD_{20} in the four groups is shown in fig 3. While the median PD_{20} generally falls in the hyper-responsive range for the atopic children with wheeze, no child who was non-atopic with cough demonstrated a median PD_{20} of <3·2 μmol methacholine. The group medians of the minimum PD_{20} and of the median PD_{20} for each subject in that group are shown in table 2. Both atopy and wheeze were associated with lower PD_{20} values when compared with non-atopy and wheeze respectively (Mann-Whitney U test, p<0·001).

The frequency distribution of the range of values of PD_{20} demonstrated by each subject over the course of 12 months, expressed in doubling doses of methacholine, is shown in fig 4. PD_{20} methacholine varied by >4 doubling dilutions in 61 (32·8%) subjects, by >5 doubling dilutions in 37 (19·9%), and by >6 in 25 (13·4%), showing that over 12 months methacholine responsiveness was not a stable phenomenon in this group, and that measurements in individuals could span the full range of doses used in testing.

Discussion

This study demonstrates a clear relationship between BHR and the presence of both atopy and the symptom of wheeze in a large group of symptomatic subjects in whom bronchial responsiveness was measured repeatedly over the course of one year. Bronchial responsiveness was shown to vary considerably in individuals over this time, almost 33% of subjects demonstrating >4 doubling dose variation in PD_{20}, although short term repeatability was good.

The children entered into this study were heterogeneous with regard to both symptom type and symptom severity. Many young children experience recurrent cough in the absence of wheezing, and the significance of this

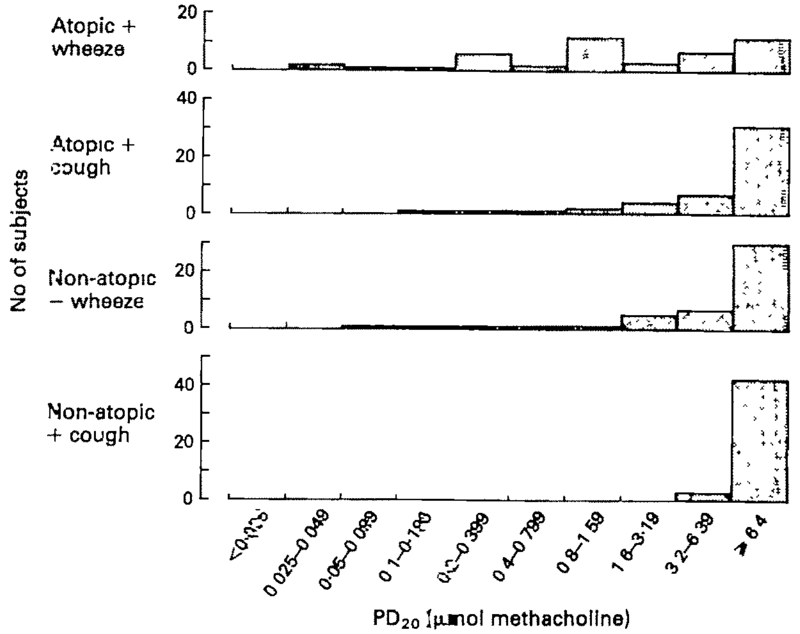

Figure 3 Frequency distribution of median PD_{20} over 12 months by symptom group

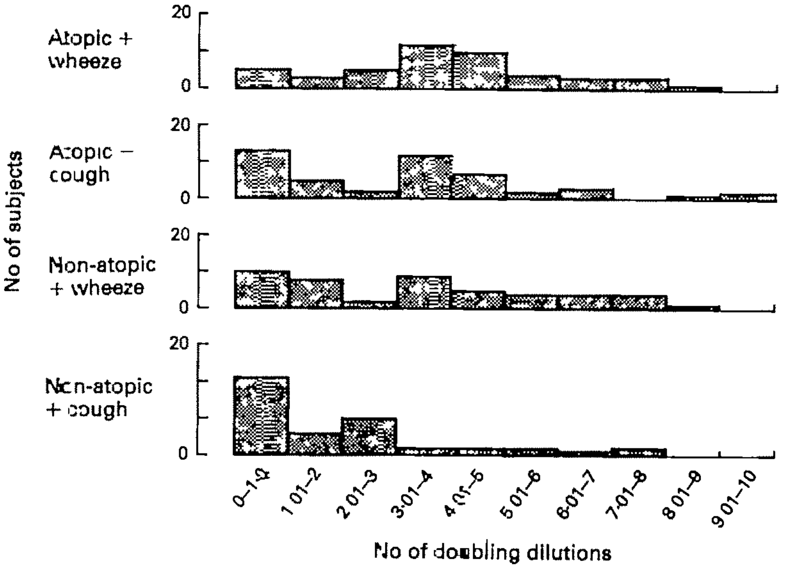

Figure 4 Range of PD_{20} demonstrated by each subject over the course of 12 months expressed in doubling dilutions of methacholine.

troublesome symptom is not clearly understood, although it is often included as a symptom of childhood asthma Thus we were eager to study subjects with cough as a sole symptom. We selected our subjects using a parent administered questionnaire, which inquired into the presence in the past 12 months of specific symptoms. We were thus able not only to avoid the predetermination of what was, or was not, asthma, but also to include in the study children with symptoms ranging in severity from mild to frankly asthmatic.

In this study, short term repeatability of the challenge procedure was found to be within 1·3 doubling doses of methacholine, which compares favourably with the findings of other workers using the method of Yan.[1 13] It was essential that, if inferences were to be made from our findings on the long term variability of methacholine responsiveness, great care was taken to ensure that the techniques used for challenge testing remained as repeatable as possible throughout the study period. Each child was tested by the same investigator at each visit, unless that investigator was unavailable due to sickness, when she was replaced by the principal investigator. Each child was tested at the same time of day on each occasion in order to exclude any effect of diurnal variation, and in the same room, to minimise environmental influences. Antiasthma medication was withheld as described, and the children were rested for 10 minutes before testing. Fresh solutions of methacholine were prepared weekly, in concentrations calculated specifically for each nebuliser and the investigator using it.

Because of the nature of the study, we obtained at least 12 PD_{20} values on all but 11 subjects and our analysis could thus be based on data collected over a 12 month period. This had the benefit of lessening the influence of the factors that can affect individual measurements of bronchial responsiveness and therefore strengthening the analyses. In spite of this, the relationship between BHR, atopy, and respiratory symptoms remained complex. Eleven per cent of those subjects with both atopy and wheeze never, at any time, demonstrated BHR, and for those demonstrating either atopy or wheeze this proportion rose to 64% and 69% respectively. These findings confirm those of Pattemore *et al* who found that 42·1% of children reported to have wheezed within the past month did not demonstrate BHR to histamine.[15] Similarly for atopy, in random population studies Welty *et al* [18] and Woolcock *et al* [19] showed no association between skin test reactivity and non-specific airways responsiveness. In asthmatic populations, Cookcroft *et al* did,[20] and Bryant and Burns[14] did not demonstrate the association of atopy with enhanced levels of bronchial responsiveness. Thus BHR appears to be an unreliable predictor of wheeze and atopy.

This study enables us to examine the relationship between BHR and respiratory symptoms in these children, selected on the basis of current symptoms. As many as 40% of asthmatic subjects who have experienced symptoms within the past 12 months do not demonstrate BHR, and approximately one third of positive responders to bronchial challenge in population surveys are asymptomatic.[5–7 15 21] These findings may be explained by the complex genetic and environmental determinants of airways responsiveness, and by the heterogeneity of the mechanisms involved. The latter include airway wall thickening leading to loss of interdependence of the airways from the surrounding alveoli and the encroachment of folds of epithelium into the bronchial lumen, smooth muscle hypertrophy, epithelial damage, disordered contractile properties of smooth muscle, exaggeration of the cholinergic mechanisms, the increased production of chemical mediators which recruit inflammatory cells, and the so called second wave mediators triggered by those inflammatory cells.[22]

Other factors that have been suggested to influence levels of responsiveness include baseline airway function,[23] and exposure to respiratory tract virus infection,[24] allergens,[25] and tobacco smoke.[26] These confounding environmental variables could influence indices of responsiveness, making a single measurement and any assumption made upon it unreliable.

Over prolonged periods of time, bronchial responsiveness has been described as being a stable phenomenon.[27] However, the findings of the present study would seem to support those of Josephs *et al*, who found that airways responsiveness in the clinical setting can vary considerably.[13] In this study, PD_{20} was found to vary by up to nine doubling doses of methacholine in individual subjects over a 12 month period, one third of subjects demonstrating a variation of >4 doubling doses. As many subjects demonstrated levels of bronchial responsiveness near or above the upper limit measured, and indeed, 48 (25·8%) children were never hyperresponsive, it would have been possible for only the most responsive subjects to exhibit the maximum degrees of variability in PD_{20}, and thus these figures are likely to underestimate the variability in PD_{20} that would be found if testing were to be performed over a greater range of methacholine concentrations.

As in the longitudinal study performed by Josephs *et al*,[13] which included as subjects both children and adults, visual examination of the charted data failed to demonstrate a temporal relationship between PD_{20} and the state of asthma described by level of PEF, day to day and diurnal variability in PEF, and symptom score. It would seem that while a broad relationship does exist between both atopy and wheeze and BHR, in *individuals* levels of bronchial responsiveness can vary greatly, and at any particular moment in time there is little correlation between PD_{20} methacholine and the severity of asthma, whether measured in terms of symptoms or changes in PEF.[8] Due to the problems posed by the large number of subjects participating in this study and their clinical heterogeneity, combined with the lack of evidence of any relationship yielded by visual inspection of the charted data, we did not analyse the data from the complete cohort for temporal relationships between symptoms and changes in PEF and bronchial responsiveness. However, such analyses on selected children will form the basis of a further publication.

Although measurement of bronchial responsiveness has useful applications as a research tool, and may be able to predict those subjects at risk of accelerated decline in lung function,[28] its lack of correlation with the clinical state of asthma and its variability over time make it less suitable for use as a test for diagnosis, assessment of treatment requirement and determination of prognosis, especially in children. Already, the small number of longitudinal studies in existence that incorporate responsiveness measurements have altered our views on the relevance of BHR to airways disease. Further studies, particularly in the early years of life, are greatly needed to establish the significance of BHR in relation to the range of diseases of childhood which are currently encompassed under the single diagnostic label of asthma.

The authors would like to thank Sandra Smith and Sue Cook, who made this work possible We would also like to thank the British Lung Foundation and the National Asthma Campaign for their funding and support

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Archives of Disease in Childhood 1992; 67: 580–585

Drug delivery from holding chambers with attached facemask

Mark L Everard, Andrew R Clark, Anthony D Milner

Abstract

There is much interest in the use of holding chambers with an attached facemask to deliver aerosols from metered dose inhalers to infants. In order to study the influence of various design factors on the dose inhaled at different tidal volumes, a model was constructed in which a Starling ventilator was used to generate an inspiratory/expiratory cycle across a filter. Sodium cromoglycate was administered via a Nebuhaler and mask, Aerochamber and mask, and a coffee cup using tidal volumes of 25, 50, and 150 ml and the dose deposited upon the filter after six breaths was assayed using an ultraviolet spectrophotometric method.

At the lowest tidal volume the high aerosol concentration in the smaller chamber enhanced drug delivery while at the highest tidal volume delivery was greatest from the larger chamber reflecting the larger dose available. Multiple breaths ensured that the dose inhaled per kilogram from each chamber was relatively large and also permitted significant drug delivery despite the introduction of a relatively large dead space between valve and filter. The dose delivered was increased by increasing the dose introduced into the chamber though not proportionately.

These devices appear likely to deliver significant quantities of aerosol to infants, though drug delivery may be enhanced by the use of an appropriate valve.

The development of a simple, effective system for delivering drugs in the form of aerosols to the lungs of infants and young children is likely to be of considerable benefit. The obvious advantage of this form of treatment over systemic administration is that a therapeutic effect can be achieved while minimising systemic side effects. Jet nebulisers have been used to deliver aerosols to infants for many years, though this form of treatment has many disadvantages. It can be very time consuming especially if required several times a day and compressors are bulky and relatively expensive. More importantly it is frequently difficult to persuade an infant to tolerate this form of treatment because jet nebulisers tend to be noisy, treatment periods are generally long, and a closely fitting mask is required for effective drug delivery. Furthermore, effective drug delivery can be greatly influenced by the type of nebuliser and the operating conditions used.[1 2]

The use of metered dose inhaler (MDI) to deliver drugs to the lungs of adults and older children is well established. Spacing devices and holding chambers have been used to overcome problems of coordination and have further advantages in that they allow the aerosol to decelerate and propellants evaporate from the drug particles. Infants and young children are unable to use these conventional devices so that a number of alternative approaches have been suggested. It has been claimed that firing a bronchodilator from a MDI directly into the buccal cavity of infants and young children can have a therapeutic effect.[3] A simple, cheap spacing device, the polystyrene coffee cup, has been in use for several years for delivering bronchodilators to young children,[4] and a larger, similar device has been used in a recent study.[5] Unfortunately these devices have a number of drawbacks in that the MDI is fired directly into the patient's face, which frequently means that then an infant will not tolerate this form of therapy and, unless firmly applied, aerosol is rapidly lost from the chamber.

Although it is more than 10 years since it was proposed that the attachment of a facemask to a holding chamber may provide a suitable delivery system for delivering aerosols to young children,[6] it is only recently that there has been a upsurge in interest in this form of treatment.[7–11] This approach has many potential advantages. The aerosol is not fired directly into the face of the infant and the use of soft facemasks ensures that they do not cause discomfort when applied to the face and hence these devices are more likely to be accepted by very young children. The seal achieved by the facemask also ensures that aerosol is retained within the chamber and as the aerosol settles out relatively slowly this will allow infants to take multiple breaths from the contained aerosol. This may significantly increase drug delivery at low tidal volumes while the usual advantages of holding chambers will also help to maximise the proportion of the inhaled dose that is subsequently deposited in the lungs.

All the systems designed so far have been adapted from systems designed for adults and older children and relatively little attention has been paid to the design factors that will maximise drug delivery to infants. The way in which factors such as aerosol concentration, total dose available, and chamber size interact to influence the total dose delivered at different tidal volumes has not been considered and is difficult to predict.

In an attempt to determine the relative importance of these complex interacting factors, a series of in vitro studies were performed in which the respiratory pattern of subjects with

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Accepted 12 December 1991

different tidal volumes were simulated using a Starling ventilator and the quantity of drug 'inhaled' was collected onto a filter and assayed.

Methods

A model was constructed to simulate the respiratory pattern of individuals with different tidal volumes. A Starling ventilator (CF Palmer) was connected via a Y connector so that air would be drawn in and subsequently exhaled through a filter (Whatman Glass Microfibre, exposed diameter 3·3 cm; fig 1). The filter paper can be considered to be the 'nose/mouth' of the model subject and the dose of drug deposited upon the filter will represent the total dose 'inhaled'. A 'face' was constructed of firm rubber so that the facemask of each device could be firmly applied to ensure a good seal. The filter was held in place at the base of a cylinder designed for the purpose. As it was not possible to measure the tidal volume across the filter, a pneumotachograph (Mercury Instruments) was placed at the level of the face and the effective tidal volume across the filter was obtained by subtracting the volume of the funnel (35 ml).

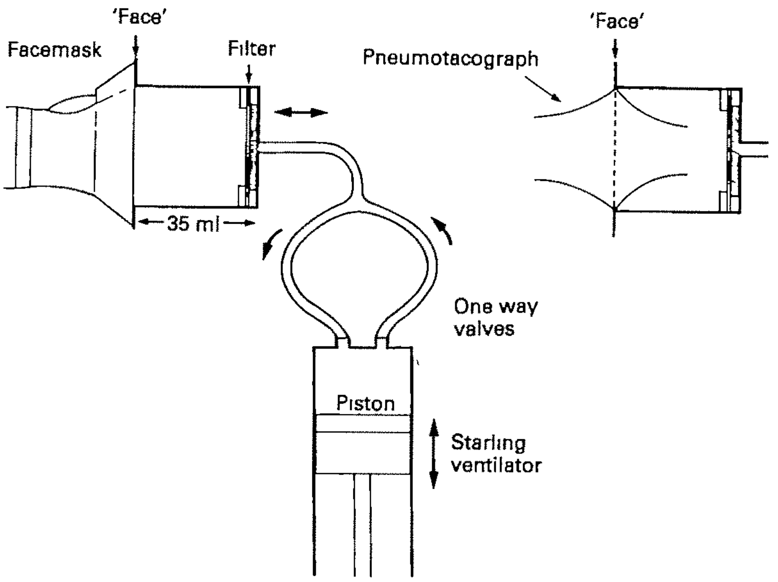

Figure 1 Model used to simulate the respiratory pattern of individuals and so study the factors influencing drug delivery from holding chambers at different tidal volumes The dose 'inhaled' by the Starling ventilator was desposited upon the filter.

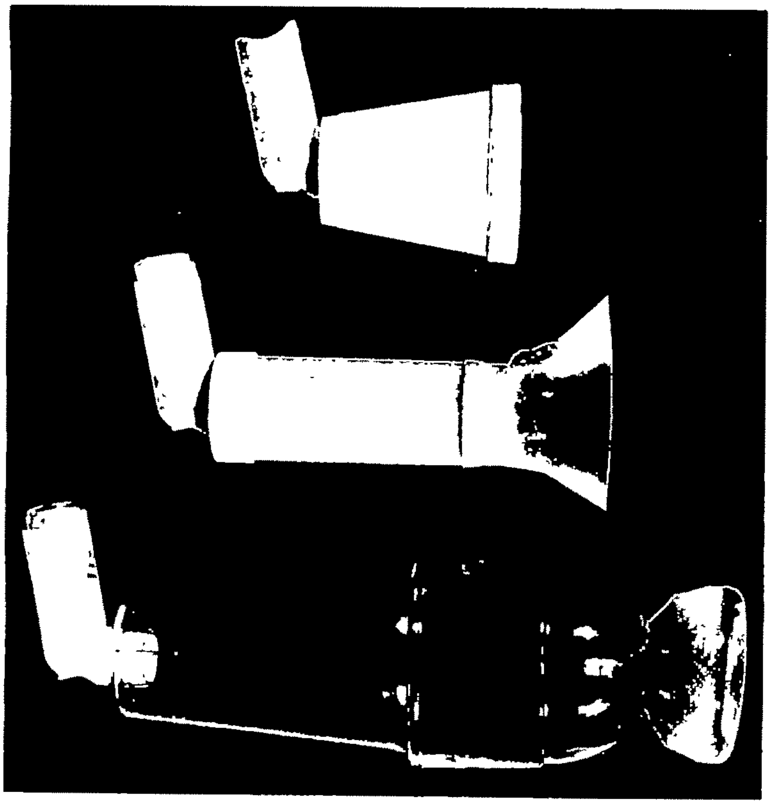

Figure 2 Devices used in these experiments From left to right: a polystyrene coffee cup, an infant Aerochamber with facemask, and a Nebuhaler with a Laerdal facemask

Experiments were performed using tidal volumes of 25, 50, and 150 ml to represent the tidal volumes likely to be seen from early infancy through early childhood. The Starling ventilator had a limited number of rate settings and an arbitrary rate of 32 was chosen for all these experiments. Inspiration occupied approximately 40% of the respiratory cycle.

Four devices were used for these experiments (fig 2); a polystyrene coffee cup, an infant Aerochamber with attached facemask (Trudell, Canada), a neonatal version of this device and a Nebuhaler (Astra) to which a size 2 Laerdal resuscitation facemask was attached, having first removed the mouthpiece. The only difference between the 'neonatal' and the 'infant' versions of the Aerochamber was that the former has a lighter valve.

The Nebuhaler was chosen to represent the larger chambers as this is the system currently used in our unit.[8] When using the Nebuhaler, the MDI was actuated with the device in the horizontal position and the valve closed, the device was then tipped so that the MDI was raised by 20°, thus allowing the valve to open by gravity and it remained open for the period of the experiment. This is the method of administration used in our unit. It was adopted because the valve appears to operate inefficiently at low flow rates. At best the valve would only partly open. Unfortunately no large volume chamber with a low resistance valve was available when these experiments were performed.

When using the coffee cup a card was placed between the coffee cup and face while the MDI was actuated to prevent direct deposition on the filter. The card was then removed immediately prior to the first inspiratory 'breath'.

For each experiment the MDI was shaken and then fired just before the start of an inspiratory phase. For these experiments each device was applied for six inspiratory/expiratory cycles, which was considered to be a reasonable period that might be tolerated by infants. To ensure that the quantity of drug deposited on the filter was adequate to obtain an accurate assay result, multiple actuations were used for each experiment. Two minutes was allowed between each actuation to ensure that the aerosol cloud in the chamber had settled out.

At the end of each experiment the quantity of drug on the filter was assayed. Sodium cromoglycate was used in these experiments because an ultraviolet spectrophotometric assay (Hewlett Packard Diode Array spectrophotometer) was available and allowed accurate quantification of drug deposition on the filter.

It was observed that at the end of each set of experiments, drug particles had been deposited within the funnel and this was therefore carefully wiped before being washed. The filter was then washed with Freon 11 to remove surfactants from the surface of drug particles deposited on it. After drying the filter was then washed with a known volume of distilled water. The absorbance at 326 nm was obtained for the resultant solution and this was then used to calculate the total quantity of drug 'inhaled' per actuation using the formula:

$$\text{Drug dose (mg)} = \frac{\text{Absorbance at 326 nm} \times \text{volume (ml)} \times 10}{\text{E} \times \text{number of actuations}}$$

The system had previously been calibrated using known quantities of sodium cromoglycate, the constant E (absorbance for 1% solution using a 1 cm path length) was 159·43. Previous experience with this method has demonstrated excellent reproducibility, this being estimated to be within 0·01 mg.

DRUG DELIVERY FROM A STANDARD DOSE AT DIFFERENT TIDAL VOLUMES

The initial experiments were designed to study quantity of drug delivered from each system at different tidal volumes. Each experiment involved 10 actuations of a 1 mg dose at two minute intervals. The quantity of drug deposited on the filter after 10 actuations was assessed when the pump was switched off (tidal volume=0) and for the tidal volumes described above.

EFFECTS OF AGITATING THE CHAMBER

In order to assess the effects of chamber movement, the experiment involving a Nebuhaler and a tidal volume of 50 ml was repeated shaking the Nebuhaler once immediately after actuating the MDI.

INCREASING THE DEAD SPACE FROM VALVE TO FILTER

For most experiments the holding chambers were held so that the mask was compressed ensuring that the chamber's valve was as close to the level of the face as possible. To assess the possible effects of a dead space, the mask of the holding chambers was held lightly against the face while a good seal was maintained. By not compressing the mask a dead space was introduced between the valve and face of approximately 50 ml for the Nebuhaler and slightly more for the Aerochamber.

INCREASING THE INITIAL DOSE INTRODUCED INTO THE CHAMBER

Experiments were performed to assess the effects of altering the aerosol concentration within a chamber using multiple actuations of a 1 mg MDI or single actuations of a 5 mg dose MDI. The 1 mg MDI was actuated two or three times before the first inspiratory cycle and this was repeated five or four times respectively. A single actuation of a 5 mg dose MDI was repeated once after two minutes.

Each experiment was repeated four times. The canister was weighed before and after each experiment to ensure that the correct amount of aerosol suspension had been delivered. The results presented represent the mean and range of the four experiments.

Finally, a mathematical model was devised in order to predict the dose that might be delivered by a chamber of different tidal volumes using different numbers of breaths. This model assumes a zero deadspace from valve to patient, a valve opening and closing efficiently, and complete mixing within the chamber once the valve is closed. It also assumes that taking a breath from the chamber does not affect the rate at which the remaining aerosol settles out.

Results

DRUG DELIVERY FROM A STANDARD DOSE AT DIFFERENT TIDAL VOLUMES

The results presented in table 1 represent the mean dose in mg delivered to the filter from 10 actuations of a 1 mg MDI from each device while using different tidal volumes. The range of results obtained from the four experiments performed under each set of conditions appears below. For each device, as the tidal volume increases, the quantity of drug delivered increased. This increase was more pronounced for the larger volume Nebuhaler. At a tidal volume of 150 ml the largest dose of drug was delivered by the Nebuhaler, while at a tidal volume of 25 ml the neonatal Aerochamber with its lighter valve delivered most drug with 5·3% of the initial dose being deposited on the filter.

CHAMBER AGITATION

Shaking the Nebuhaler reduced the dose delivered to the filter from 0·93 mg to 0·25 (0·15–0·36) when the tidal volume was set at 50 ml.

EFFECTS OF INCREASING THE DEAD SPACE

Introducing a dead space of approximately 50 ml between the valve and the face reduced the dose deposited upon the filter when using a 50 ml tidal volume from 0·93 mg to 0·43 (0·39–0·48) mg when using the Nebuhaler. For the Aerochamber increasing the dead space as described reduced the dose delivered to the filter from 1·15 mg to 0·42 (0·37–0·48) mg.

Table 1 Mean (range) dose deposited on the filter after 10 actuations of a 1 mg sodium cromoglycate MDI delivered by each of four devices and different tidal volumes

	Tidal volume (ml)			
	0	*25*	*50*	*150*
Aerochamber (1 mg×10)	0·027 (0·024–0·030)	0·33 (0·29–35)	1·15 (1·08–1·24)	1·41 (1·33–1·4[illegible])
Neonatal Aerochamber (1 mg×10)	0·035 (0·028–0·039)	0·53 (0·47–0·58)	—	—
Coffee cup (1 mg×10)	0·031 (0·028–0·033)	0·27 (0·23–0·30)	0·86 (0·76–1·02)	—
Nebuhaler (1 mg×10)	0·008 (0·007–0·008)	0·29 (0·26–0·32)	0·93 (0·91–0·97)	1·55 (1·48–1·6[illegible])

EFFECTS OF INCREASING THE INITIAL DOSE INTRODUCED INTO THE CHAMBER

The mean dose deposited upon the filter after two actuations of a 5 mg MDI via the Aerochamber using a 50 ml tidal volume was 0·70 (0·67–0·72) mg while the equivalent dose via the Nebuhaler was 0·74 (0·71–0·77) mg. The dose delivered to the filter from five administrations of 2×1 mg via the Nebuhaler with a tidal volume of 50 ml was 1·02 (0·93–1·10) mg while four administrations of 3×1 mg delivered 0·844 (0·79–0·91) mg to the filter. These results are presented in table 2 in terms of the dose delivered to the filter per administration of the chosen combination and the figure in brackets is that dose delivered to the filter expressed as a percentage of the administered dose.

Table 2 Mean (%) total dose of sodium cromoglycate deposited on the filter from a single administration using initial doses of 1, 2, 3, or 5 mg administered by Nebuhaler or Aerochamber. A tidal volume of 50 ml was used

	1 mg	*2×1 mg*	*3×1 mg*	*5 mg*
Aerochamber (mg)	0·12 (11·5)	—	—	0·35 (7)
Nebuhaler (mg)	0·09 (9·3)	0·20 (10·1)	0·21 (0·7)	0·37 (7·3)

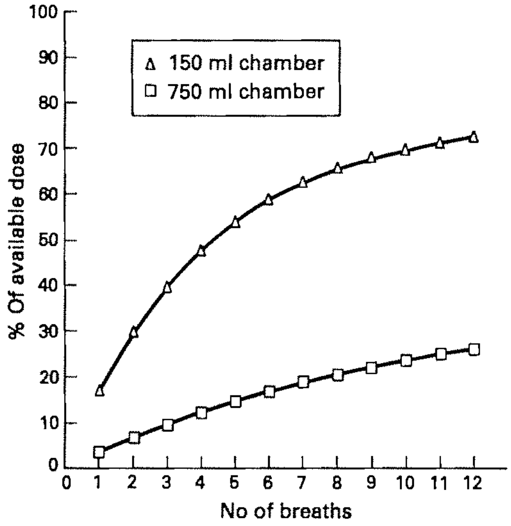

Figure 3 Comparison of the relative delivery efficiency of a 150 ml and 750 ml chamber with a tidal volume of 25 ml and a respiratory frequency of 32 breaths per minute derived from the mathematical model. The 'available' dose represents that contained within the chamber after actuation of the MDI.

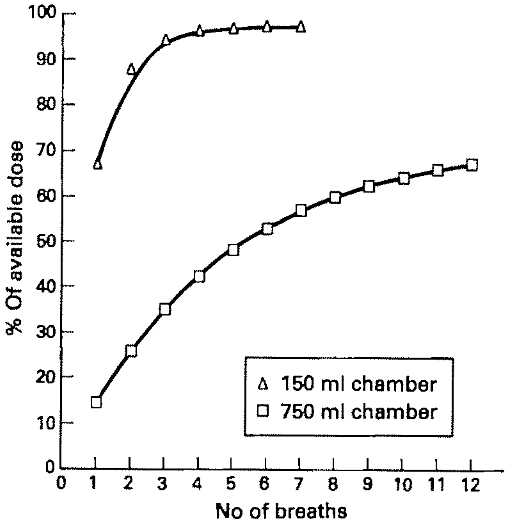

Figure 4 Comparison of the relative delivery efficiency of a 150 ml and 750 ml chamber at a tidal volume of 100 ml and a respiratory frequency of 32 breaths per minute derived from the mathematical model. The 'available' dose represents that contained within the chamber after actuation of the MDI.

MATHEMATICAL MODEL

The fraction of the maximum obtainable dose as a function of breath number and tidal volume was found to be of the form:

$$M/M_{max}=V_t/V.\sum_{i=1}^{i=n}(1-[V_t/V])^{i-1}\exp(-\lambda(i-1)/\gamma)$$

Where: M/M_{max}=dose inhaled as fraction of initial dose available, V_t=tidal volume, γ=breathing frequency, V=chamber volume, i=n=number of breaths, and λ=half life of aerosol held in chamber (see footnote for derivation of the above equation).

Figures 3 and 4 represent typical graphs obtained using this equation; λ was assumed to be 15 seconds based upon previous experimental work. It can be seen that at both tidal volumes drug delivery reaches a plateau earlier for the smaller chamber. In order to calculate the total dose delivered in a given number of breaths, the dose available within the chamber must be known and, as noted above, this is dependent upon both the design of the chamber and the dose delivered into it from the MDI.

Discussion

Holding chambers with an attached facemask potentially offer a major advance in the treatment of respiratory disease in infancy. If they are shown to be effective then their ease of use should ensure that they are widely accepted. It is important therefore that the factors likely to influence the effectiveness of drug delivery are considered so that maximum benefit can be obtained. This model represents a new approach to the problem of assessing the influence of various design features upon drug delivery. The advantages of this model are that the Starling ventilator permits us to use a reproducible tidal volume and respiratory rate so that direct comparisons can be made when changing from one device to another.

The dose deposited upon the filter in this model would represent the total dose inhaled by a subject at these tidal volumes, respiratory rate, and inspiratory flows. The pattern of deposition within the respiratory tract of this inhaled dose will be influenced by a number of patient variables such as airway obstruction and technical factors such as the size of drug particles administered. Particle size will be determined predominately by the MDI formulation, though it will be optimised when using a holding chamber. The single most important variable influencing the dose of drug reaching the lungs that is amenable to manipulation is the total dose that is inhaled from each administration of drug. These experiments allow us to consider some of the factors that might maximise the dose inhaled and hence maximise the dose reaching the lower respiratory tract.

VALVE DESIGN

In adults it has been shown that during acute asthma the expiratory flow of a patient may be too low to close the valve of a Nebuhaler and hence aerosol is blown out of the device during expiration.[12 13] It is claimed that this may contribute to the poor response sometimes seen with these devices in severe acute asthma. A recent study measuring pressure changes within the chambers claimed that the valves of both the Nebuhaler and Volumatic (Allen and Hanbury) will open and close at the low flows generated by infants.[14] Unfortunately this does not necessarily correlate with drug delivery as a partially open valve is likely significantly to impair drug delivery. The importance of a valve that operates effectively at low tidal volumes was emphasised in the experiments comparing the neonatal and infant versions of the Aerochamber at a tidal volume of 25 ml.

DEAD SPACE

Not surprisingly drug delivery fell dramatically by introducing a relatively large dead space. Perhaps more surprising was that despite such a relatively large dead space, drug deposition on the filter was still in the order of 4·2% of each 1 mg dose administered. The likely explanation for the significant drug delivery that occurred despite the relatively large dead space is that during the first breath even if little or no drug reaches the filter, aerosol is drawn into the mask. This aerosol then mixes with expired air and some aerosol is subsequently inhaled from the facemask during the next breath while more drug is being drawn into the mask and so on.

AEROSOL CONCENTRATION AND TOTAL DOSE AVAILABLE

Though the interaction of tidal volume with aerosol concentration, chamber size, and total dose available in determining drug delivery is complex, it can be clarified to some extent by considering the results of these experiments. Increasing the aerosol concentration can be altered in two ways. Either a larger dose can be introduced into the same chamber or the same dose can be introduced into a different sized chamber. Both of these options will also alter the total dose available.

Increasing the dose introduced into a chamber

From table 2 it would appear that increasing the dose introduced into a chamber appears an effective way of increasing drug delivery per treatment, though the delivered dose did not increase directly in proportion to the initial dose used. For the Nebuhaler a 3·8-fold increase in the dose delivered was achieved when using a single actuation from a 5 mg MDI while only a 3-fold increase was obtained when using the Aerochamber. This is probably due to relatively greater drug loss from impaction on the walls of the chamber when using the larger dose. When multiple 1 mg doses were introduced into the Nebuhaler with a tidal volume of 50 ml, two 1 mg actuations did double the dose delivered but further actuations produced very little additional drug delivery. This is probably due to particles of relatively large mass and velocity being introduced into the chamber and causing increased deposition due to turbulence. Another factor which may be contributing is that actuating the MDI in rapid succession may not permit the valve to fully fill with suspension before it is next actuated. This would imply that a single larger dose is more effective in raising the aerosol concentration within a chamber than multiple small doses.

Chamber size

One aspect of design that is much more difficult to predict is the effect of changes in chamber volume, which in turn influences both the available dose of aerosol and the concentration of aerosol within that chamber. In clinical studies it has been shown that for older children[15] and adults[16] large cone shaped chambers are more effective than a MDI used alone while the Aerochamber appears to be as effective as an optimally used MDI.[17] Isotope studies have shown that 37% of the dose introduced into a Nebuhaler may be inhaled by adults,[18] while the comparable figure for the Aerochamber is around 14%.[17] Thus although the total dose of aerosol available within the larger chamber is greater, it is distributed in five times the volume and hence the initial aerosol concentration is less.

The result of the experiments presented in table 1 suggest that at low tidal volumes the high initial aerosol concentration within the Aerochamber is a major factor influencing the dose delivered, but as the tidal volume increases the larger total dose available in the larger chamber becomes more important. These differences are likely to be relatively unimportant clinically as it should be noted that in terms of drug delivery per kilogram body weight an infant is likely to receive considerably more than an adult. An infant weighing approximately 6–7 kg might have a tidal volume of 50 ml[19] yet drug delivery to the filter was in the order of 10%, a 70 kg adult might at best inhale around 37% from a large chamber and considerably less from the smaller one. Clinical studies have shown clinical benefit in this age group when using both large and small chambers.[8 10]

For infants taking multiple breaths from a chamber, predicting the dose inhaled is difficult. If an infant's tidal volume is 50 ml it will extract approximately one third of the available aerosol during the first breath from the 150 ml volume Aerochamber, but only approximately one fifteenth of that available within the 750 ml volume Nebuhaler. Because such a relatively large amount has been extracted during the first breath the aerosol concentration within the Aerochamber available for the next breath will fall to a much greater extent than that within the large chamber. This calculation is further complicated by the fact that the aerosol will settle out progressively with time. Results using the mathematical model support the suggestion that a high aerosol concentration of the smaller chamber will tend to enhance drug delivery at the lowest tidal volumes but that the higher total dose in the larger chamber enhances drug delivery as the tidal volume increases.

These experiments allow us to assess design factors that might maximise the dose of drug inhaled. There are several factors specific to this form of treatment in infants that may influence the proportion of the inhaled dose that might be deposited within the lungs. Nasal breathing by infants may increase deposition in the upper respiratory tract. If this were shown to be a major problem it could be overcome using a mask similar to the Laerdal mask, which can be gently placed over the upper lip occluding the nasal passages and thus ensuring that the infants breath through their mouth.

Infants will obviously not hold their breath and this will tend to reduce deposition in the peripheral airways by sedimentation. A recent study in older children found a greater improvement in forced expiratory volume in one second at 10 minutes by taking five breaths from a Nebuhaler than by taking two breaths with a five second breath holding after each, though the peak improvements were similar.[20] At low tidal volumes the greater total dose inhaled by taking multiple breaths will probably more than compensate for the reduced time allowed for deposition. The effect of crying cannot be predicted, the greater volume and hence dose inhaled may be off set by increased drug loss in the device and upper airway due to inertial impaction.

In summary the design of a chamber intended for use with infants should have a valve that operates efficiently at very low flow rates if a valve is required. The dead space from valve to patient should be minimised by good mask design. Using multiple doses or, more effectively, a single larger dose can increase the aerosol concentration within the chamber and so increase drug delivery per breath. However, the increase in drug delivery is not necessarily proportional to the increase in dose. Agitation of the chamber will greatly reduce drug delivery.

Both large and small chambers would appear to deliver significant amounts of drug at these low tidal volumes. However, a small chamber would seem to be more appropriate in that they are easier to handle while trying to hold a wriggling infant, they are generally less intimidating for the infant and they deliver at least as much, if not more, drug at these low tidal volumes. Finally in terms of drug delivery per kilogram body weight infants would appear likely to inhale a greater dose than an adult from a standard metered dose. The proportion of the inhaled dose that reaches the lungs remains to be determined.

We would like to thank Ms Julie Stammers and Dr David Walker for their helpful comments during the preparation of this manuscript.

Dr Everard was supported by the National Asthma Campaign

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Footnote

If the aerosol concentration within the chamber is C_0 and the unhaled tidal volume is V_t then the drug inhaled on the first breath is:

$$M_0=V_t.C_0$$

Subsequently a volume of clear air equal to V_t will be drawn into the chamber and the concentration will fall to:

$$C_1=C_0(V-V_t/V).\exp.(-\lambda T)$$

where V is the volume of the chamber and the exponential term represents the time decay of the aerosol cloud; λ=concentration half life, and T=is the time between inhalations.

The dose delivered on the second breath will thus be:

$$M_1=V_t.C_0(V-V_t/V).\exp(-\lambda T)$$

T is in effect $i-1/\gamma$ where γ is the breathing frequency since T=0 at the first breath. Extending this analysis for third and subsequent breaths the total dose inhaled in n breaths can be obtained by the expression:

$$M=V_t.C_{i=1}^{i=n}\Sigma(1-[V_t/V]).^{i-1}\exp.(-\lambda(i-1)/\gamma)$$

In terms of the maximum dose obtainable from the device becomes:

$$M/M_{max}=V_t/V_{i=1}^{i=n}\Sigma(1-[V_t/V]).^{i-1}\exp(-\lambda(i-1)/\gamma)$$

Archives of Disease in Childhood 1992; 67: 586–591

Drug delivery from jet nebulisers

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Abstract

Maximising the rate of drug delivered in particles small enough to reach the lower respiratory tract from jet nebulisers may allow treatment times to be reduced and thus improve the acceptability of this form of treatment, particularly in very young patients. The role of various technical factors such as driving gas flow (DGF) in determining the rate of drug delivery was studied by constructing a model to simulate the respiratory pattern of individuals with different tidal volumes using a Starling ventilator and filter. Sodium cromoglycate was nebulised under a variety of operating conditions and the dose deposited on the filter was assayed. Tidal volumes of 50 and 400 ml were used at a frequency of 32 breaths per minute.

Increasing the DGF from 4 to 8 l/minute produced a 264% increase in the rate of drug output but only a 32% increase in aerosol concentration. The mass of drug contained within droplets <5 µm increased from 26·8% to 70·8% of the total. The resultant increase in rate of drug delivery to the filter was 34% for a tidal volume of 50 ml and 79% for a tidal volume of 400 ml though the dose contained within droplets <5 µm increased by 4-fold at 50 ml tidal volume and by more than 5-fold at the higher tidal volume. Halving the solution concentration halved the rate of drug delivery. Increasing the tidal volume 8-fold from 50 to 400 ml resulted in an increase in the rate of drug deposition upon the filter of only 2·2 to 3-fold depending upon the DGF so that substantially more drug per ml inhaled was delivered at the lower tidal volume.

These results are explained by considering factors that influence the rate of drug delivery. At low tidal volumes the rate of drug delivery at a given respiratory rate is dependent on the tidal volume and aerosol concentration. At high tidal volumes it is dependent upon aerosol concentration and volume of available aerosol and is essentially independent of tidal volume.

Jet nebulisers have been used for many years to deliver aerosols to the lower respiratory tract. The doses used for a wide variety of drugs have largely evolved empirically and current recommendations for operating the nebuliser are largely directed towards maximising the quantity of drug leaving the nebuliser chamber. Unfortunately the time required to nebulise a dose may be long and hence regular treatment may therefore be inconvenient and, particularly in young patients, poorly tolerated. If the rate at which drug is delivered to the lower respiratory tract could be increased, treatment times could be reduced leading to improvements in the acceptability and efficacy of this form of treatment.

Radioisotope studies have shown that around 10% of the dose placed in the chamber of a jet nebuliser may reach the lungs of adults,[1–4] though this is greatly influenced by the nebuliser used and the way in which it is operated.[1 5] Current recommendations for the use of jet nebulisers are based on studies which have looked at individual aspects of nebuliser performance such as total output and the way in which these are influenced by altering technical factors such as fill volume or driving gas flow (DGF).

Although these experiments remain the basis for current recommendations, there are a number of problems associated with them. Many of the studies have simply assessed drug output on the basis of the change in weight within the nebuliser,[6–8] which is inaccurate because of the significant evaporation of water during nebulisation.[9 10] More recent studies have addressed this problem by assaying the quantity of drug left in the nebuliser chamber at the end of a period of nebulisation and subtracting this from the initial dose.[11]

More fundamentally, these studies fail to consider the ways in which technical factors such as the DGF interact with each other and with patient factors such as tidal volume in determining the rate at which drug is delivered to the patient. For example these studies have shown that increasing the DGF will increase both the rate of drug output[6 10] and the proportion of drug within the aerosol contained in droplets <5 µm in size.[12–14] These studies do not consider the influence of changes in tidal volume with age upon either the total dose inhaled or the relative dose delivered when corrected for body weight.

As it would not be possible to assess the effects of these changes in children because of ethical considerations, a new approach was devised using an in vitro model to determine how change in tidal volume might interract with the various technical factors influencing the output of jet nebulisers to influence the rate at which drug is inhaled. By combining these results with those obtained with a laser particle sizer, the rate at which drug contained within droplets <5 µm was delivered under each set of conditions was calculated.

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Accepted 12 December 1991

Methods

A model was constructed in order to simulate the respiratory pattern of individuals with different tidal volumes. For this a Starling ventilator (C F Palmer) was connected via a Y connector in such a way as to allow air to be drawn in and exhaled out through a filter (Whatman Glass Micro fibre, exposed diameter 3·3 cm; fig 1). The filter paper can be considered to be the 'nose/mouth' of the model. The dose of drug deposited upon the filter represents the total amount of drug inhaled.

A 'face' was constructed from firm rubber so that the facemask of the nebuliser could be firmly applied. To minimise deposition of drug due to aerosol flowing directly into the mask and impacting on the filter, the filter was held in place at the base of a cylindrical funnel, designed for this purpose. A cylinder with a relatively large diameter (4·2 cm) was chosen to ensure that effective mixing would occur within the funnel and facemask. The funnel also allowed calibration of the tidal volume across the filter. It was not possible to place a pneumotachograph within the funnel at the level of the filter and hence it was placed at the level of the face. The effective tidal volume at the filter being obtained by subtracting the volume of the funnel (35 ml) from the measurement obtained at the face.

The Starling ventilator had a limited number of settings and a rate of 32 breaths per minute was chosen for these experiments. No attempt was made to consider the effects of change in respiratory rate and a single setting was chosen to minimise the variables when comparing results. Inspiration occupied approximately 40% of the respiratory cycle. Tidal volumes of 50 and 400 ml were chosen as typical of an infant of approximately 9 months of age and an adult subject. An infant or adult mask was used in these experiments, as appropriate.

The experiments were performed using a single Cirrhus nebuliser (Intersurgical) chosen at random. This is the make most widely used in our unit and it is typical of the commonly used jet nebulisers. Preliminary experiments had demonstrated variations in output of up to 20% when testing nebulisers of the same make while the mass median diameter and percentage of droplets less than 5 µm in size at a given DGF also varied considerably. Similar results have been described previously.[7 14] The driving gas was supplied by a cylinder of air and the flow was measured using a flow meter appropriately calibrated for compressed air (BOC Medishield).

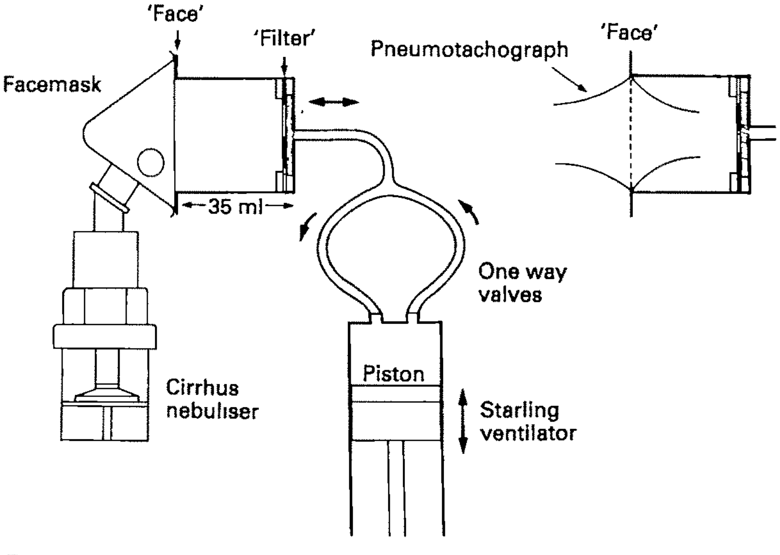

Figure 1 Model used to simulate the respiratory pattern of individuals and so study the factors influencing the rate of drug delivery from jet nebulisers at different tidal volumes. The dose 'inhaled' by the Starling ventilator was deposited upon the filter.

Sodium cromoglycate solution (20 mg in 2 ml) was used in these experiments because an ultraviolet spectrophotometric assay (Hewlett Packard Diode Array spectrophotometer) was available and allowed accurate quantification of drug quantities on the filter and in the nebuliser chamber at the end of each experiment. To obtain the quantity of drug left within the nebuliser chamber and that deposited on the filter, both were first washed with known volumes of distilled water and the absorbance at 326 nm was obtained for the resultant solution. This was then used to calculate the total quantity of drug using the formula:

$$\text{Drug dose (mg)} = \frac{\text{Absorbance at 326 nm} \times \text{volume (ml)} \times 10}{E}$$

The system had previously been calibrated using known concentrations of sodium cromoglycate, the constant E (absorbance for a 1% solution using a 1 cm path length) was 159·43. Previous experience with this method has demonstrated excellent reproducibility, this being estimated to be within 0·01 mg.

In most experiments 4 ml of 1% sodium cromoglycate solution were placed within the nebuliser chamber which allowed continuous nebulisation throughout a five minute period. This time was chosen as this is probably the longest period one might reasonably expect a small child or infant to sit still. Experiments were performed using DGFs of 4, 6, and 8 l/minute with a tidal volume of 50 ml, DGFs of 4 and 8 l/minute at a tidal volume of 400 ml, and a single study at 8 l/minute with the Starling pump turned off. In addition, the effects of moving the mask 1 and 2 cm away from the model face on the delivered dose was examined using a DGF of 8 l/minute and a tidal volume of 50 ml. As a more concentrated solution of sodium cromoglycate was not available the effects of altering solution concentration were studied by diluting 2 ml of solution with 2 ml of normal saline when using a DGF of 8 l/minute and a tidal volume of 50 ml. Each experiment was performed four times. The nebuliser was weighed before and after each experiment. The results are presented as the mean and range of the four experiments performed under each set of conditions.

Particle size measurements were performed with a Malvern 2600 laser particle sizer using the Fraunhofer diffraction model. For aqueous aerosols this method permits accurate sizing of droplets as they are generated and avoids the problems of drying associated with methods such as cascade impactors which tends to over estimate the quantity of aerosol in the 'respirable range'.[15]

Results

The mean (range) quantity of sodium cromoglycate leaving the nebuliser during a five minute period of continuous nebulisation increased from 4·61 mg (4·25–5·11) when using a DGF of 4 l/minute to 12·13 mg (11·38–12·96) at the higher DGF.

The effect on total dose deposited on the filter or 'inhaled' of altering the DGF at different tidal volumes is shown in fig 2. With the Starling ventilators switched off (tidal volume= 0), very little drug, 0·029 mg (0·026–0·033) was deposited upon the filter when a 1% solution was nebulised for five minutes using a DGF of 8 l/minute. At 50 ml tidal volume, increasing the DGF from 4 to 8 l/minute produced a 34% increase in the quantity of drug deposited upon the filter in a five minute period. The dose deposited increased from 0·91 mg (0·87–0·96) when using a 4 l/minute DGF to 1·02 mg (0·98–1·07) at 6 l/minute and 1·21 mg (1·18–1·28) at the 8 l/minute. The same change in DGF produced a larger increase in quantity of drug depositing upon the filter of 79% when the tidal volume was set at 400 ml. The dose deposited upon the filter increased from 2·09 mg (0·1·98–1·22) to 3·74 mg (3·57–3·94). The dose deposited on the filter when nebulising 4 ml of a 0·5% solution of sodium cromoglycate for five minutes was 0·57 mg (0·53–0·59) when using a DGF of 8 l/minute and a tidal volume of 50 ml. The effects of increasing the DGF on particle size are shown in the table. As the DGF increased the mass median diameter fell and the percentage of particle mass within the aerosol contained in droplets less than 5 µm in size increased. These results apply only to the individual nebuliser used in these experiments.

Figure 3 shows the appreciable effect of moving the facemask away from the face. At only 1 cm from the face while still directing the aerosol stream towards the filter the dose delivered was only 0·49 mg (0·46–0·51) using a tidal volume of 50 ml and a DGF of 8 l/minute. At a distance of 2 cm the reduction was even greater with only 0·18 mg (0·17–0·2) reaching the filter.

As sodium cromoglycate is a solution, it is possible to combine the results of total drug inhaled with those obtained using the particle sizer to infer the quantity of drug deposited upon the filter contained in droplets <5 µm during each experiment. The results obtained are shown in fig 4.

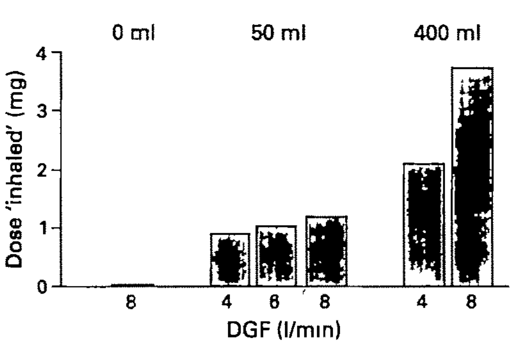

Figure 2 Mean dose of drug deposited upon the filter at tidal volumes of 0, 50, and 400 ml when 1% sodium cromoglycate was nebulised for five minutes using DGFs of 4, 6, and 8 l/minute.

Aerosol mass median diameter and mass of droplets <5 µm in size expressed as percentage of the total droplet mass measured when using DGFs of 4, 6, and 8 l/minute. Results were obtained using a Malvern 2600 laser particle sizer

DGF (l/min)	*Mass median diameter (µm)*	*% Of droplet mass <5 µm*
4	7·0	26·8
6	4·9	50·1
8	3·6	70·8

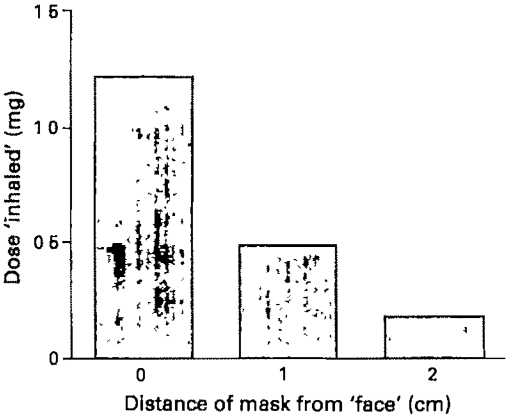

Figure 3 The dose deposited upon the filter in a five minute period of nebulisation with increasing distance between the nebuliser facemask and the 'face' of the model when using a DGF of 8 l/minute and a tidal volume of 50 ml.

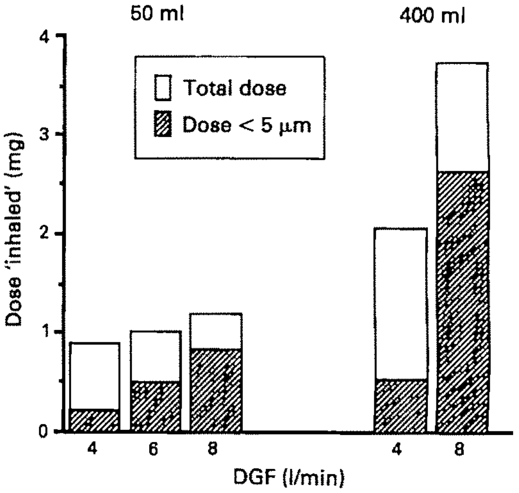

Figure 4 Total dose and dose contained within droplets <5 µm in size delivered to the filter at tidal volumes of 50 and 400 ml when using different DGFs.

From these results a model was constructed in order to consider the factors influencing the rate of drug delivery at different tidal volumes at an arbitrary respiratory rate (fig 5 and 6) while consideration of the interaction of the various technical resulted in a flow diagram illustrated in fig 7.

Discussion

In this study we have used a novel experimental approach in an attempt to elucidate the complex interaction of technical and patient factors which influence the rate of drug delivery to the

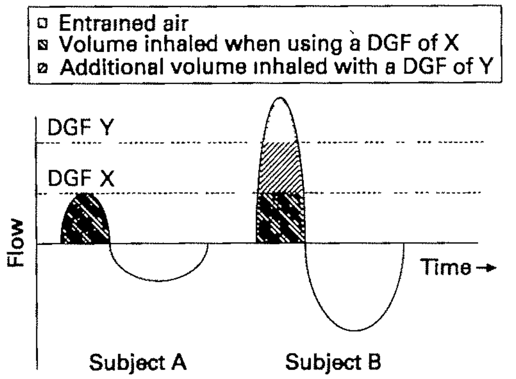
□ Entrained air
▨ Volume inhaled when using a DGF of X
▨ Additional volume inhaled with a DGF of Y
DGF Y
DGF X
Flow
Time
Subject A
Subject B

Figure 5 Diagram illustrating factors affecting the rate of drug delivered to individuals at a given respiratory rate. At low tidal volumes (A), the dose is dependent upon the tidal volume and aerosol concentration. At high tidal volumes (B), air entrainment occurs and hence the dose is dependent upon the aerosol concentration and the available volume of aerosol. It is largely independent of tidal volume.

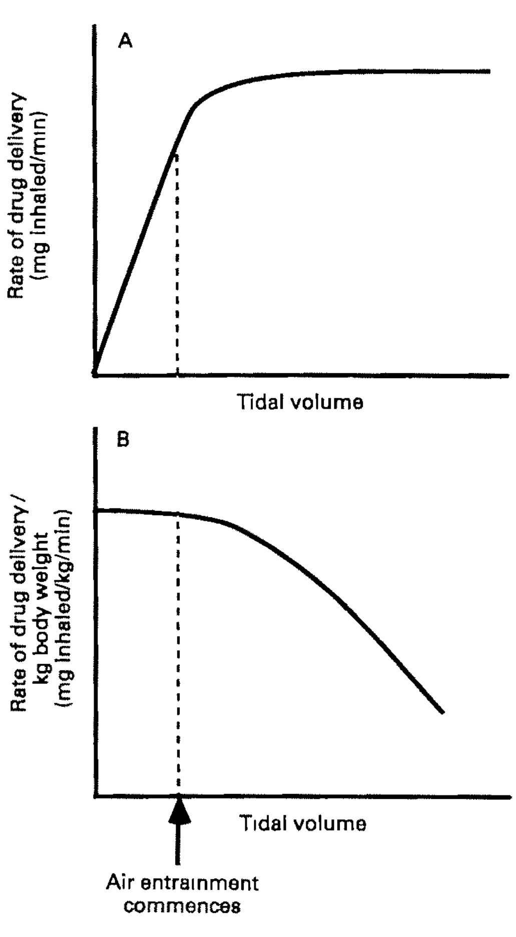

Figure 6 Diagramatic representation illustrating the effect of increasing tidal volume upon (A) the rate at which drug is inhaled from a jet nebuliser and (B) the rate at which drug is inhaled corrected for body weight.

lungs of infants and adults when using jet nebulisers. The model we constructed allows us to simulate the respiratory pattern of individuals and determine the total dose of drug that might be inhaled from a jet nebuliser in a given period of time. As the tidal volume and respiratory rate are reproducible the effect upon the total dose inhaled of altering technical factors, such as DGF or solution concentration, can be assessed accurately. Conversely the effect of changes in tidal volume upon the total dose inhaled can be assessed under a given set of nebuliser operating conditions. By considering these results in conjunction with measurements of particle size we can infer the quantity of drug contained in droplets smaller than 5 μm in size inhaled in a given time and hence obtain a guide to the rate at which the drug is likely to be delivered to the lower respiratory tract from a nebuliser when using a particular set of operating conditions. The actual dose reaching the lungs of an individual will of course be further influenced by other factors such as the degree of airway obstruction beyond the scope of this study.

These experiments have produced some surprising and, at first sight, contradictory results. A 264% increase in the drug output produced by doubling the DGF resulted in only a 34% increase in drug delivery at a tidal volume of 50 ml and a larger 79% increase at a tidal volume of 400 ml. An 8-fold increase in tidal volume from 50 to 400 ml resulted in an increase in the rate of drug reaching the filter of only 2·2–3-fold depending upon the DGF used. In order to explain these results we must consider the factors that influence the rate of drug delivery at high and low tidal volumes (fig 5) and the way in which technical factors such as DGF influence these determinants of drug delivery (fig 7). From fig 5 it is apparent that the total dose inhaled per breath at low tidal volumes is the product of the aerosol concentration and tidal volume. At the higher tidal volume the peak inspiratory flow exceeds the DGF and hence air entrainment occurs. Consequently the dose inhaled is dependent upon the aerosol concentration and volume of aerosol available which in turn is determined by the DGF. The dose inhaled per breath becomes largely independent of the subject's tidal volume as can be seen diagramatically in fig 6. The total dose inhaled increases linearly as tidal volume increases until air entrainment occurs. Further increases in tidal volume result in little additional drug being inhaled while the volume of air entrained rapidly increases effectively diluting the concentration of drug within the aerosol. As there is a fairly constant linear relationship between weight and tidal volume from infancy through to adulthood of 7–10 ml/kg,[16] correcting these results for tidal volume or body weight means that the infant would receive a considerably larger total dose than the adult shown diagramatically in fig 7. Infants have a higher minute volume per kilogram body weight than an adult,[16] hence the dose per kg inhaled per minute is likely to be even higher in infants. A study carried out at the same time as this work indicated that air entrainment commences at the tidal volumes seen in early childhood.[17]

AEROSOL CONCENTRATION

The concentration of aerosol generated by a jet nebuliser is a major determinant of the rate at which drug is inhaled at all tidal volumes. Though drug output increased by a factor of 2·64 when the DGF was doubled, the concentration of aerosol only increased by a third since the volume of aerosol generated had doubled. At a high DGF further increases may result in a fall in aerosol concentration as the rise in output tends to plateau.

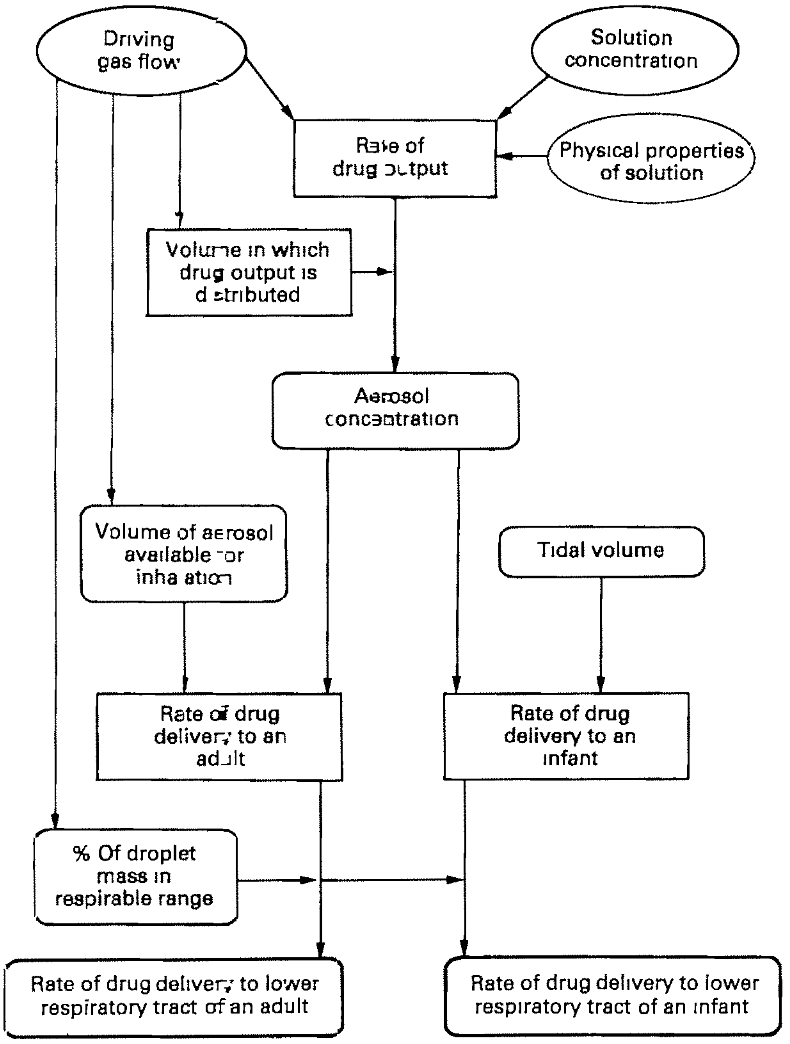
Driving gas flow
Solution concentration
Rate of drug output
Physical properties of solution
Volume in which drug output is distributed
Aerosol concentration
Volume of aerosol available for inhalation
Tidal volume
Rate of drug delivery to an adult
Rate of drug delivery to an infant
% Of droplet mass in respirable range
Rate of drug delivery to lower respiratory tract of an adult
Rate of drug delivery to lower respiratory tract of an infant

Figure 7 Diagram illustrating the complex interaction of technical factors that influence drug delivery to patient through factors such as aerosol concentration and particle size. The design of a nebuliser affects the particle size distribution and rate of output, therefore further changes have to be considered if changing make of nebuliser.

When using a 0·5% solution drug delivery in a five minute period was slightly less than half that when using a 1% solution. For solutions, the concentration of drug within each droplet generated by a jet nebuliser reflects the concentration of the solution from which it is generated. Hence, halving the concentration of the sodium cromoglycate solution effectively halved the concentration of drug within each droplet generated. Providing the change in solution concentration does not significantly alter the rate at which droplets leave the nebuliser by altering factors such as viscocity and surface tension, the quantity of drug and hence aerosol concentration generated by the nebuliser will be halved. The eventual total output when 2 ml of saline were added to 2 ml of drug solution was greater. However, diluting the 1% solution significantly reduced the rate of drug delivery and the time required for nebulisation to dryness increased substantially. Designing nebulisers to operate with smaller solution volumes and to have a low dead volume would be advantageous. Physical properties such as surface tension and viscosity will influence the rate of drug and will be dependent upon the drug used

VOLUME OF AEROSOL AVAILABLE

The volume of aerosol available during the inspiratory phase of each breath was determined by the DGF. Doubling the DGF at the lower tidal volume increased the volume of aerosol lost directly into the atmosphere and therefore did not effect the rate of drug delivery. At the higher tidal volume, increasing the DGF increased the volume of aerosol available hence reducing the volume of entrained air required and directly contributed to the increase in drug delivery. It should be noted that at high tidal volumes the DGF will alter the rate of drug delivery but it will not have a major influence on the total quantity of drug inhaled when nebulising a given volume of solution to dryness as the dead volume is largely independent of DGF.[6] If one third of the respiratory cycle is inspiratory then one third of the total dose discharged from the nebuliser will be inhaled irrespective of DGF.

The use of facemasks will have relatively little effect on the dose inhaled, although a reservoir to contain the aerosols generated during the expiratory phase will increase drug delivery in subjects with high tidal volumes by increasing the volume of aerosol available and so reduce air entrainment.

INTERACTION OF TOTAL INHALED DOSE AND PARTICLE SIZE

Jet nebulisers are designed to deliver drug to the lower respiratory tract. The dose reaching this site will be dependent upon both the total dose inhaled and the fraction of that dose contained in droplets small enough to penetrate into the lower respiratory tract (fig 6). It is believed that droplets 1–5 μm in size are most likely to pass through the upper airway and be deposited in the lung peripheries.[18] Increasing the DGF from 4 to 8 l/minute has altered the rate of drug output, the volume in which this is distributed, the aerosol concentration, the volume of aerosol available during the inspiratory phase, and the size distribution of the droplets. The net effect is that the dose deposited upon the filter contained within droplets less than 5 μm in size, that is the respirable range, increased 4-fold at the lower tidal volume and more than 5-fold at the higher tidal volume (fig 7). These results could not have been predicted from considering a single effect such as change in the rate of drug output.

CLOSELY FITTING FACEMASKS

We often observe nurses and mothers attempting to hold a facemask in front of a struggling toddler. Figure 3 illustrates the dramatic effects of holding the facemask even a very small distance in from the face. The amount of drug inhaled was greatly reduced. At only 2 cm drug delivery was only 15% of that when a closely fitting mask was used. If this were repeated using a low DGF, the quantity of drug inhaled in droplets less than 5 μm in size is likely to be minimal and this may partly explain the poor response to nebulised treatment often seen when treating infants.

It is likely that drugs such as β_2 sympathomimetics are used in supermaximal doses when delivered by jet nebulisers.[1 19] This probably explains their efficacy despite the great variations in operating conditions used to nebulise them.[20–22] For other drugs such as antibiotics it is possible that therapeutic effects can be enhanced by increasing the dose delivered. By considering factors which influence the rate of drug delivery it may be possible to minimise treatment periods and so improve compliance and hence efficacy.

In these experiments we have considered the effects of altering DGF and solution concentration upon the rate of drug delivery at low and high tidal volumes. This approach could be used to assess the effects of altering many other parameters such as solution viscosity and nebuliser design and so improve the effectiveness of this form of treatment.

We would like to thank Ms Julie Stammers and Dr David Walker for their helpful commments during the preparation of this manuscript

Dr Everard was supported by the National Asthma Campaign

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Archives of Disease in Childhood 1992; 67: 592–594

Role of infection in the middle lobe syndrome in asthma

Chaim Springer, Avraham Avital, Natan Noviski, Chana Maayan, Ilana Ariel, Paul Mogle, Simon Godfrey

Abstract

Twenty one children with asthma aged 1·0–10·5 years (mean (SD) 3·3 (2·5) years) were admitted to the hospital to evaluate pulmonary right middle lobe or lingular collapse lasting one to 12 months (mean (SD) 4·4 (3·8) months). Seven children had mild asthma and were treated with inhaled β_2 agonists as needed. Nine had moderate asthma treated with either sodium cromoglycate or slow release theophylline. Five had severe asthma treated with inhaled steroids. Each child underwent fibreoptic bronchoscopy under local anaesthesia and a bronchoalveolar lavage. Differential cell counts of the lavage fluid revealed predominance of neutrophils in 12 patients (57%). In nine of these patients cultures grew pathogenic bacteria, mainly *Haemophilus influenzae* and *Streptococcus pneumoniae*. There was no correlation between the severity of asthma and a positive bacterial culture. There was also no correlation between the duration of the right middle lobe collapse and a positive culture. We conclude that longstanding right middle lobe collapse in asthmatic children is often associated with bacterial infection.

Pulmonary segmental or lobar collapse is a common complication of childhood asthma. It has been reported that about 5–10% of all children hospitalised with acute asthmatic attacks had radiographic evidence of lobar collapse, the right middle lobe being involved most frequently.[1 2]

The incidence of infection in the lobar collapse in asthmatic patients is not clear. Hopkirk and Stark reported five asthmatic patients with repeated episodes of pulmonary atelectasis.[3] Sputum culture grew *Haemophilus influenza* in only one patient, and in four patients bronchial aspirates were negative for bacteria or fungi. Dees and Spock could not find any specific diagnostic help in sputum or bronchoscopic aspirates in 30 children with right middle lobe collapse.[4] Also, Billing and Darling reported normal flora from bronchial secretions in 11 children with right middle lobe atelectasis.[5]

The purpose of this study was to examine the incidence of infection in the right middle lobe collapse in a group of asthmatic children.

Patients and methods

Over a period of four years, 21 asthmatic children (16 boys and five girls) aged 1–10·5 years were admitted to Hadassah University Hospital for the evaluation of right middle lobe (20 patients) or lingular (one patient) collapse (table 1). The duration of the collapse ranged from one to 12 months. A history of recurrent febrile episodes was positive in 13 patients. Regular antiasthmatic treatment in these patients consisted of inhaled beclomethasone dipropionate or budesonide in five children classified as severe asthma, sodium cromoglycate in eight and slow release theophylline in one classified as moderate asthma, and inhaled β_2 agonists as needed in seven children classified as mild asthma.

Table 1 Patient characteristics, bronchoalveolar differential cell counts, and culture results

Patient No	*Sex*	*Age (years)*	*Culture*	*BAL % cell count*			
				Neutrophils	*Lymphocytes*	*Macrophages*	*Eosinophils*
1	M	2·0	*H influenzae*	95		5	
2	M	2·0	*H influenzae*	62		38	
3	M	3·0	Negative	68	26	6	
4	M	1·0	Negative	50		50	
5	M	1·5	*S pneumoniae*	50		50	
6	M	5·5	*H influenzae*	77	3	20	
7	M	1·5	*H influenzae*	95		5	
8	M	2·0	Negative	20	20	60	
9	F	1·0	Negative	20	10	70	
10	F	4·0	Acinetobacter sp	85		15	
11	M	4·0	Negative	5	10	85	
12	M	9·0	*H influenzae*	68		32	
13	M	1·5	Negative	30		70	
14	M	4·0	*Branhamella catarrhalis*	25		75	
15	M	10·5	Negative	25	25	45	5
16	M	3·0	Negative	5		95	
17	M	3·5	*H influenzae*	75		25	
18	F	3·0	Negative	70	20	10	
19	F	4·0	*S pneumoniae*	70	10	20	
20	M	2·0	Negative	20		80	
21	M	2·0	Negative	30		70	

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Accepted 17 January 1992

Bronchoscopies were performed as part of our routine investigations to evaluate longstanding lobar collapse, using a 3·6 mm fibreoptic bronchoscope (Olympus BF 3C20). Sedation was achieved using oral chloral hydrate (50–100 mg/kg and intravenous pethidine 1–2 mg/kg. Lignocaine hydrochloride up to 5 mg/kg was used for local anaesthesia of the airways. Heart rate and oxygen saturation by pulse oximetry were monitored during the procedure. Bronchoalveolar lavage of the right middle lobe or the lingula was performed using buffered saline. The recovered bronchoalveolar lavage (BAL) fluid was cytocentrifuged (Hettich Universal) for 10 minutes at 3000 rpm. The preparation was fixed in 96% ethyl alcohol and stained by haematoxylin and eosin for differential cell count. Aliquots of the fluid were Gram stained and cultured for bacteria. Samples were cultured for bacteria only if squamous epithelial cells were not seen on Gram stains.

Analysis by χ^2 and *t* tests was performed when appropriate; p value was considered significant if $<0·05$.

Results

Airway anatomy was normal in 20 patients. Narrowing of the orifice of the right middle lobe bronchus was observed in one patient. Mucopurulent secretions from the right middle lobe bronchus were observed in three patients and from the lingula in one patient. Differential cell counts of the BAL revealed a predominance of neutrophils (≥50% of the total cell count) in 12 out of the 21 patients (57%), (table 1). In nine of these 12 patients and in patient 14 with BAL neutrophils of 25% (48% of all patients), cultures resulted in a poor growth of an upper respiratory tract flora and a heavy growth of a single pathogenic bacterium (*H influenzae*, β-lactamase negative and *Streptococcus pneumoniae* being the most frequent). In all the other patients cultures resulted only in a poor growth of upper respiratory flora.

There was a significant correlation between a positive culture and the predominance of neutrophils in the BAL fluid (table 2). No correlation was found between a positive BAL culture and a history of recurrent febrile episodes, nor was there any correlation with white cell count in peripheral blood (mean (SEM) 9120 (780) in patients with positive cultures and 11244 (1166) in patients with negative cultures, p=0·154). No correlation was found between the severity of asthma and a positive bacterial culture (table 3). In addition, no correlation was found between the duration of the collapse and a positive BAL culture (4·0 (1·4) months in patients with positive cultures and 4·5 (1·0) months in patients with negative cultures, p=0·73).

All the patients with positive cultures were treated with appropriate antibiotics according to sensitivity. In all but one patient (patient 19) complete resolution of the collapsed lobe was observed within a few weeks (up to three months).

Table 2 Correlation between BAL cultures and differential cell counts. Values are mean (SEM) in percentages

Predominant BAL cells	*Positive culture*	*Negative culture*
Neutrophils	70 (7)*	26 (6)†
Macrophages	26 (7)*†	63 (7)†*

*Significance by unpaired *t* test: †p=0·0001, **p=0·001

Table 3 Bronchoalveolar lavage cultures related to severity of asthma

Asthma severity	*Positive culture*	*Negative culture*
Mild	3	4
Moderate	4	5
Severe	3	2

χ^2 test p=0·82

Discussion

Collapse of the right middle lobe or the lingula is well described in asthmatics,[1–3] although no satisfactory explanation of the phenomenon has yet been found. The term right middle lobe syndrome was first described by Graham and colleagues and was thought to be an obstructive atelectasis due to the compression of the right middle lobe bronchus by enlarged peribronchial lymph nodes.[6] However, enlarged peribronchial lymph nodes are likely to be found mainly in middle lobe bronchiectasis and are probably not the cause of the collapse in asthmatic patients. Culiner suggested that impaired or absent collateral ventilation is the main cause for the increased incidence of right middle lobe atelectasis.[7]

Our study may shed new light on the pathogenesis of the right middle lobe collapse in asthmatic children by showing that it is associated with bacterial infection in about 50% of the patients examined. This proportion of positive cultures may have been underestimated due to the widespread use of antibiotics by the primary physicians. It is possible that BAL specimens were contaminated by bacteria from the upper respiratory tract introduced to the lower airways by the bronchoscope. It has been shown that the presence of less than 1% squamous epithelial cells and more than 10 colony forming units in BAL fluid were associated with bacterial infections of the lower respiratory tract.[8 9] In our study we cultured specimens only if squamous epithelial cells were not detected in Gram stains and considered as a positive culture only those with a heavy growth of a single pathogen. Moreover, all the BAL samples with positive cultures (except in patient 14) were associated with a predominance of neutrophils. In three patients (numbers 3, [illegible], 18) BAL differential cell counts revealed 50% or more of neutrophils and negative cultures. This may be due to a recent unreported antibiotic treatment and probably not to bronchial inflammation caused by asthma since it has been reported that neutrophils are only slightly increased in stable asthma.[10] It should be noted that our findings are different from those of Hopkirk and Stark[3] and those of Billing and Darling[5] who found either sterile cultures or normal flora in most patients. However, Dees and Spock although stating that they could not find any specific diagnostic help in sputum or bronchial aspirates, report positive bacterial cultures from bronchial aspirates in 11 out of 29 (38%) examined.[4]

In the present study, in all patients except one complete resolution of the collapsed lobe was observed within three months. As this was an open study we cannot be sure that the resolution in the patients with a positive culture was due only to the antibiotic treatment. However, we believe that infection should be considered in every patient with a longstanding lobar collapse unresponsive to aggressive antiasthmatic treatment, and an appropriate antibiotic should be added to these patients. Failure to treat a longstanding lobar collapse may result in chronic infection and bronchiectasis.[11 12]

As no correlation was found between positive cultures and recurrent febrile episodes or leucocytosis in the peripheral blood, such criteria cannot differentiate infected from non-infected patients. The incidence of infection was similar among the mild, moderate, and severe asthmatic patients (table 3). As the severe asthmatics were receiving inhaled corticosteroids, it suggests that such treatment does not predispose children to pulmonary bacterial infections.

In conclusion, we have shown that longstanding right middle lobe collapse in asthmatic children is often associated with bacterial infections. It is suggested that every asthmatic child with this complication should be treated with aggressive antiasthmatic treatment and chest physiotherapy. Failure of such an approach will justify additional antibiotic therapy to treat *H influenzae* and *S pneumoniae* as the most common pathogens.

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*The duration of infusion should be at least 8 hours.

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Archives of Disease in Childhood 1992; **67**: 595–599

HIV-1 infection and perinatal mortality in Zimbabwe

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Accepted 29 January 1992

Abstract

As part of a survey of the causes of perinatal mortality at Mpilo Maternity Hospital, 220 neonatal deaths and the mothers of 221 stillbirths were tested for HIV-1 antibodies. The HIV positive rate in neonatal deaths was 23·6% (95% confidence interval (CI) 18·0 to 29·2%), significantly higher than 15·4% (95% CI 10·6 to 20·1%) in stillbirths. Perinatal deaths from congenital malformations, birth asphyxia, pregnancy induced hypertension, placental abruption, and other non-infectious causes had similar low HIV positive rates averaging 8·1% (95% CI 3·9 to 12·3%). Deaths from septicaemia had a significantly greater rate of 39·3% (95% CI 27·0 to 51·6%) and the highest rate of 72·2% (95% CI 51·5 to 92·9%) was found in deaths from congenital infection other than syphilis, indicating that maternal HIV infection predisposes to neonatal septicaemia and congenital infection. Unexplained stillbirths also had a significantly greater rate of 22·4% (95% CI 10·7 to 34·1%), presumably because some died from unrecognised infection. The rate in deaths from congenital syphilis was 17·4% (95% CI 9·6 to 25·2%), indicating a significant but weak association between these two sexually transmitted diseases in Bulawayo. The rate in deaths from hyaline membrane disease was not significantly greater at 15·0% (95% CI 6·0 to 24·0%). By predisposing to infection, maternal HIV infection was estimated to increase the stillbirth rate by 1·6 times and the neonatal mortality rate by 2·7 times. It predisposed equally to early and late onset neonatal septicaemia, but more to infection from streptococci and staphylococci than from Gram negative enterobacteria. HIV positive deaths from congenital infection had respiratory distress and usually intrauterine growth retardation, hepatosplenomegaly, and congenital pneumonia on lung histology.

In Zimbabwe and other Central African countries, the epidemic of heterosexually transmitted HIV-1 infection is now a major health problem. Studies have estimated that between 7% and 39% of HIV positive mothers transmit the infection to their babies.[1–8] The lowest transmission rate was found in Europe among asymptomatic intravenous drug abusers who rarely breast fed,[1] whereas the highest rate was found in two studies in Central Africa among breast feeding mothers, one sixth of whom had symptoms of HIV disease.[7 8] Most infected babies become ill in the first year but rarely in the neonatal period.[2 9 10] In Europe and America HIV positive mothers had stillbirth and neonatal mortality rates of about 10/1000 births, similar to those in control HIV negative mothers,[2 10–12] but had higher infant mortality rates of around 20/1000 births.[2 4] In contrast HIV positive mothers in Central Africa had stillbirth rates of about 20/1000 births, similar to those in control mothers,[7 8 13] but had higher neonatal mortality rates of 60/1000 births, compared with 15/1000 in controls,[7 13] and a much higher infant mortality rate of 150/1000 births, compared with 25/1000 in controls.[7] This indicates that infected babies die earlier in Africa and suggests that, in addition to being a major cause of infant mortality,[7] HIV infection may be a significant cause of neonatal mortality, at least in urban communities with a high prevalence of infection.

A survey of the causes of perinatal mortality in Bulawayo, Zimbabwe, found that congenital syphilis, birth asphyxia, hyaline membrane disease, neonatal septicaemia, congenital malformations, pregnancy induced hypertension, and placental abruption together accounted for 80% of the deaths.[14] HIV infection predisposes infants to septicaemia,[15 16] and it was therefore postulated to be a factor contributing to the high rate of neonatal septicaemia in Bulawayo. One study in Africa found that the proportion of HIV positive mothers that delivered prematurely was greater than in controls,[17] and another study showed that prematurity was associated with HIV seropositivity,[17] suggesting that infection might predispose to hyaline membrane disease by causing prematurity. In five studies, three from Africa[8 13 18] and two from Europe[11] and America,[13] however, no increase in prematurity compared with controls was found. It is now established that HIV infection does not cause congenital malformations,[2 4 5 7 18 19] and there is little or no evidence that it is associated with birth asphyxia,[7 12] pregnancy induced hypertension,[12] or placental abruption. However, being a sexually transmitted disease, it may be associated with syphilis.

In order to determine what if any contribution maternal HIV infection makes to the high perinatal mortality rate in Bulawayo, the HIV status of consecutive neonatal deaths and stillbirths was tested and from this the proportion of deaths from each cause that were HIV positive was calculated. A high proportion would suggest that HIV infection contributes to the cause of death, whereas a low proportion would indicate no contribution.

Patients and methods

Over a seven month period, as part of a survey of the causes of perinatal mortality at Mpilo Maternity Hospital in Bulawayo,[14] blood taken for syphilis serology from all neonatal deaths and from the mothers of all stillbirths was anonymously tested for HIV-1 antibodies using two enzyme immunoassay tests (Abbott Recombinant HIV-1 EIA and either Vironostika anti-HTLV-III MicroELISA or Du Pont HIV-1 ELISA). If the two tests gave discrepant results, both tests were repeated until concordant results were obtained. As the tests detect IgG antibodies that cross the placenta, a positive result in the infant or mother was taken to indicate maternal HIV infection. The results were kept confidentially and were not made available to the mothers or staff of the hospital. In order to prevent a bias in determining the cause of death, the results were not matched to the patients until the end of the survey when the causes of death had already been established, as described previously.[14] The results were analysed by calculating the proportion, with 95% confidence intervals (CI), of deaths from each cause that were HIV positive. These proportions were then compared using χ^2 tests.

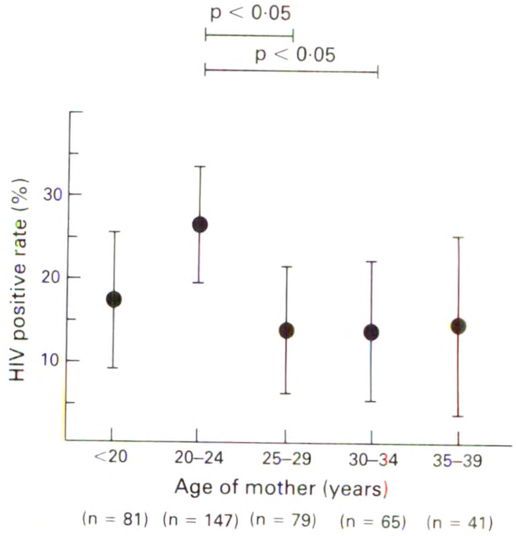
Results

Over the seven month period, HIV serology results were obtained in 220 out of a total of 235 (94%) neonatal deaths and in 221 out of a total of 271 (82%) stillbirths. Forty two of the 50 stillbirths with no results were delivered in the first and last months of the survey, and in the intervening five months results were obtained in 96% of stillbirths. Seven of the neonatal deaths with results were in fact babies who died after 28 days, but were included because they died before discharge from the neonatal unit. The proportions of perinatal deaths attributed to each cause were not significantly different in the sample with HIV results compared with the whole group of deaths analysed over the 12 month survey period ($p>0·10<0·90$).[14]

Out of the total of 441 perinatal deaths tested, 86 were HIV positive and 355 were HIV negative, indicating that 19·5% (95% CI 15·8 to 23·2%) of perinatal deaths were HIV positive. The proportion of neonatal deaths that were HIV positive was 23·6% (95% CI 18·0 to 29·2%), significantly greater than the proportion of 15·4% (95% CI 10·6 to 20·1%) found in stillbirths ($p<0·05$), suggesting that maternal HIV infection is more likely to contribute to neonatal deaths than to stillbirths. The results from the stillbirths and neonatal deaths were combined and analysed according to the mother's age (figure) and the cause of death (table 1).

As shown in the figure, the proportion of mothers that were HIV positive was significantly greater in the 20–24 year group than in either the 25–29 or the 30–34 year group, suggesting that women under 25 years are most at risk of acquiring HIV infection.

The proportions of perinatal deaths that were HIV positive are shown for each cause of death in table 1. Deaths from congenital malformations, birth asphyxia, pregnancy induced hypertension, placental abruption, and other non-infectious causes excluding hyaline membrane disease all had similar low proportions, with a combined HIV positive rate of 8·1% (95% CI 3·9 to 12·3%). This rate was used as a baseline against which to compare the rates in deaths from the remaining causes. The rate in



Relation between mothers' age and HIV positive rate. Bars represent 95% CI of the rate. Fourteen mothers over 39 years were tested and three were HIV positive.

Table 1 The HIV positive rate for each cause of perinatal death

	Stillbirths		*Neonatal deaths*		*Perinatal deaths*		*HIV+ rate (%)*	*95% CI*	χ^2	*p Value*
	HIV−	*HIV+*	*HIV−*	*HIV+*	*HIV−*	*HIV+*				
Congenital malformations	10	2	16	1	26	3	8·1	3·9 to 12·3		
Birth asphyxia	38	5	24	1	62	6				
Pregnancy induced hypertension	21	2	0	0	21	2				
Placental abruption	17	1	0	0	17	1				
Other non-infectious causes[*]	9	0	13	1	22	1				
Hyaline membrane disease	0	0	51	9	51	9	15·0	6·0 to 24·0	2·34	>0·1
Congenital syphilis	48	8	28	8	76	16	17·4	9·6 to 25·2	5·01	<0·05
Unexplained stillbirths	38	11	0	0	38	11	22·4	10·7 to 34·1	7·67	<0·01
Neonatal septicaemia†	6	4	31	20	37	24	39·3	27·0 to 51·6	31·14	<0·001
Congenital infection	0	1	5	12	5	13	72·2	51·5 to 92·9	53·66	<0·001
Total	187	34	168	52	355	86				

The HIV positive rate for each of the last five causes was compared using χ^2 tests with the average rate for the first five causes.

[*] Other non-infectious causes of stillbirths were postmaturity (n=4), diabetes (n=3), placenta praevia (n=1), and cord knot (n=1) and of neonatal deaths were meconium aspiration syndrome (n=7), birth trauma (n=3), kernicterus (n=2), milk aspiration (n=1), and posthaemorrhagic hydrocephalus (n=1).

†Ten fresh stillbirths who died after prolonged rupture of membranes or maternal fever with features of amnionitis were presumed to have had septicaemia and were therefore included in neonatal septicaemia. In only one was a blood culture obtained and it grew *Escherichia coli*. Six of the neonatal deaths from septicaemia had typical features of septicaemia but negative blood cultures. The HIV positive rate in the 46 blood culture positive deaths from septicaemia was 39·1% (95% CI 25·0 to 53·2%), very similar to the rate in the group as a whole.

hyaline membrane disease was not significantly greater at 15·0% (95% CI 6·0 to 24·0%) whereas the rate in congenital syphilis was significantly greater but was only 17·4% (95% CI 9·6 to 25·2%). Unexplained stillbirths also had a significantly greater rate of 22·4% (95% CI 10·7 to 34·1%). However, the rate in neonatal septicaemia was much greater at 39·3% (95% CI 27·0 to 51·6%) and the highest rate of 72·2% (95% CI 51·5 to 92·9%) was found in deaths caused by congenital infections other than syphilis and early onset septicaemia. Details regarding these 18 deaths have been reported separately.[14] Of the 13 that were HIV positive, three died after 28 days from AIDS with failure to thrive and multiple episodes of septicaemia, nine died in the first 14 days with features suggesting congenital infection, and one was a fresh small for gestational age stillbirth with hepatosplenomagaly. Of the five who were HIV negative, one had congenital tuberculosis with miliary foci of caseous necrosis in the lung and liver containing acid fast bacilli and few inflammatory cells, one probably had herpes simplex infection with a vesicular skin rash, microabscesses in the lung, and massive hepatic necrosis, and three had non-specific features of congenital infection.

After completion of this study all neonatal deaths from septicaemia and congenital infection were HIV tested and the parents counselled. Over the next seven months, 47 out of 51 neonatal deaths from septicaemia were tested and 22 were HIV positive giving a rate of 46·8% (95% CI 32·5 to 61·1%). These deaths were combined with those from the previous seven month study period in order to determine if there were any differences between HIV positive and HIV negative cases in birth weight, age at death, or bacteria cultured. As shown in table 2, no significant differences in birth weight or age at death were found, but there were significant differences in the bacteria responsible. The HIV positive rate in deaths from streptococcal and staphylococcal septicaemia was 52·5% (95% CI 37·0 to 68·0%), significantly higher than the rate of 23·8% (95% CI 10·9 to 36·7%) found in deaths from Gram negative enterobacteria (p<0·01). In three HIV positive cases, haemophilus, bacillus, and acinetobacter species were isolated. In the latter two cases the same organism was grown in two separate blood culture samples, and in eight HIV positive cases with typical features of septicaemia no bacteria were grown. Nine out of 11 babies who died from pulmonary or gastrointestinal haemorrhage caused by septicaemia were HIV positive.

During the seven months after this study all neonatal deaths with features of congenital infection were HIV positive. Over the whole 14 month period, all eight surviving infants discharged from the neonatal unit with features of congenital infection were HIV tested and three were HIV positive. Table 3 gives a summary of the clinical, laboratory, and histological features of all the HIV positive and HIV negative infants with congenital infection excluding the five cases of AIDS, congenital tuberculosis, and probable herpes simplex infection described above. Most infants in both groups were small for gestational age with respiratory distress, hepatosplenomegaly and less commonly petechiae and if they survived after 48 hours developed conjugated hyperbilirubinaemia, anaemia, and thrombocytopenia. There were five infants with microcephaly and other features of congenital infection, all of whom survived to discharge. Two of these were HIV positive and both had high rubella IgG titres which increased further on repeat testing. Two of the three HIV negative cases had rubella IgG titres of 1:64 or greater but repeat titres were not obtained. Six surviving infants with microcephaly but no other features of congenital infection were HIV tested and all were negative. Rubella IgG titres obtained in four of them were 1:64 or greater in all cases and one on repeat testing had an increased titre. Serological tests for cytomegalovirus, toxoplasmosis, and herpes infections were incomplete and produced no diagnostically useful results.

In order to determine how much maternal

Table 2 Comparison of HIV positive and HIV negative deaths from septicaemia

	HIV+ (n=42)		*HIV− (n=57)*		*p Value*
Mean (SD) birth weight (g)	1634 (774)		1398 (676)		>0·1
Age at death (days):					
1–2	22		24		
3–7	10		20		>0·1
8–28	8		11		
>28	2		2		
Streptococcus group:					
B	7	21	6	19	
D	4		4		
A	1		1		
C	1		0		
Staphylococcus aureus	4		5		
Staphylococcus epidermidis	4		3		<0·01
Klebsiella	8	10	21	32	
Escherichia coli	2		5		
Coliforms	0		2		
Proteus	0		3		
Pseudomonas	0		1		
Haemophilus	1		0		
Bacillus	1		0		
Acinetobacter	1		0		
No growth	8		6		

This table excludes the nine stillbirths included in table 1 who were presumed to have died from septicaemia but had no blood culture samples obtained.

Table 3 Comparison of HIV positive and HIV negative infants with congenital infection

	HIV+	*HIV−*
No (No who died)	18 (15)	8 (3)
Mean (SD) birth weight (g)	1779 (759)	2162 (629)
Age at death (days):		
1–2	11	1
3–7	2	1
8–28	2	0
>28	0	1
Features:		
Small for gestational age	13/18	6/8
Respiratory distress	15/17	4/8
Hepatomegaly	11/18	7/8
Splenomegaly	9/18	8/8
Petechia	5/18	4/8
Convulsions	3/17	1/8
Microcephaly	2/18	3/8
Microphthalmia	1/18	0/8
Hydrops	0/18	1/8
Anaemia	5/8	3/7
Thrombocytopenia	5/7	3/6
Conjugated hyperbilirubinaemia	4/7	4/8
Septicaemia	2/17	1/8
Histology:		
Generalised atelectasis	2/9	1/3
Congenital pneumonia	5/9	1/3
Meconium aspiration	1/9	0/3
Hepatitis	1/9	2/3

HIV infection increases perinatal mortality, the prevalence of HIV infection in mothers delivering at Mpilo Maternity Hospital was first estimated. In mothers without syphilis this rate should be similar to the 8·1% found in perinatal deaths not associated with HIV infection, that is congenital malformations, birth asphyxia, pregnancy induced hypertension, placental abruption, and other non-infectious causes excluding hyaline membrane disease, which may be associated with HIV infection. In mothers with syphilis this rate should be similar to the 17·4% found in perinatal deaths from congenital syphilis. During the survey 11·0% of mothers attending antenatal clinics in Bulawayo had positive syphilis serology and using this figure the prevalence of HIV infection among mothers delivering at Mpilo Maternity Hospital was estimated to be 9·1%. This rate should be less than the rate in mothers resident in Bulawayo because some of the deliveries at the hospital are referred from rural areas with a lower prevalence of HIV infection. Using this estimate and the HIV positive rates for each cause of death given in table 1, the number of HIV positive and negative deliveries, stillbirths, and neonatal deaths were calculated over the whole 12 month survey period.[14] From these figures, HIV positive mothers were found to have a perinatal mortality rate 2·1 times greater, a stillbirth rate 1·6 times greater, and a neonatal mortality rate 2·7 times greater than HIV negative mothers.

Discussion

This study demonstrates that maternal HIV infection contributes to perinatal mortality in Zimbabwe by predisposing to neonatal septicaemia and congenital infection. There is no evidence that HIV infection increases the risk of congenital malformations, birth asphyxia, pregnancy induced hypertension, placental abruption, and other non-infectious causes excluding hyaline membrane disease.[2 4 5 7 12 18 19] The HIV positive rate in deaths from these causes was 8%, reflecting the prevalence of HIV infection in mothers without syphilis delivering at Mpilo Maternity Hospital. This rate is similar to the rates of 6% and 12% found in 1987 in mothers in Kinshasa, Zaire[7] and Lusaka, Zambia[8] respectively. The HIV positive rate in deaths from neonatal septicaemia and congenital infection was significantly greater at 39% and 72% respectively, indicating that maternal HIV infection predisposes to deaths from these conditions. The rate in unexplained stillbirths was also significantly greater at 22% presumably because some of these stillbirths died from unrecognised infection. The rate in deaths from congenital syphilis was significantly increased at 17%, indicating a weak association between these two heterosexually transmitted diseases in Bulawayo. In Nairobi no association was found.[19] Unlike HIV infection, untreated early syphilis greatly increases perinatal mortality and is the leading cause of perinatal death in Bulawayo, but could be effectively controlled by screening all mothers at about 20 weeks and treating those with positive syphilis serology.[14] The rate in deaths from hyaline membrane disease was not significantly increased at 15%, although perhaps a larger study would show a significant association if HIV infection predisposes to preterm delivery.[7 17]

Deaths from septicaemia and congenital infection occur mainly after birth and HIV positive mothers were estimated to have a neonatal mortality rate of 2·7 times greater and a stillbirth rate 1·6 times greater than HIV negative mothers. In Kinshasa HIV positive mothers had more than four times the neonatal mortality rate but a similar stillbirth rate to HIV negative controls.[7] Most infected infants born to HIV positive mothers do not become sick until after the neonatal period,[18] however, and the major impact of HIV infection is to increase infant mortality rather than perinatal mortality. In Kinshasa HIV positive mothers had more than six times the infant mortality rate of HIV negative controls.[7] Unlike syphilis, HIV infection is far more difficult to control. In Bulawayo, like other parts of Central Africa,[18] young women under the age of 25 years are most at risk and for health education to have any effect it should be directed at adolescents at school.

Maternal HIV infection could predispose to neonatal septicaemia by either reducing passively acquired immunity from the mother without infecting the baby or reducing the baby's own immunity by direct infection. It predisposes equally to early onset septicaemia acquired from the mother and to late onset hospital acquired septicaemia, but predisposes more to septicaemia caused by Gram positive cocci than to septicaemia caused by Gram negative enterobacteria. These observations suggest that a reduction in passively acquired immunity especially to streptococcal and staphylococcal infection is important. HIV infection may predispose to neonatal septicaemia simply by causing preterm delivery, but this is unlikely to be important because the mean birth weight of HIV positive and HIV negative deaths from septicaemia were similar and significantly greater than the mean birth weight of deaths from hyaline membrane disease ($p<0{\cdot}001$), who had a significantly lower HIV positive rate ($p<0{\cdot}01$). In Kinshasa chorioamnionitis was common in mothers with AIDS but was rare in asymptomatic HIV positive mothers.[7]

Maternal HIV infection could predispose to congenital infection by reducing maternal immunity to rubella, cytomegalovirus, toxoplasmosis, and other pathogens allowing them to infect the fetus more easily, or the HIV virus could infect the fetus and be responsible on its own for the features of congenital infection. Most of the features found in HIV positive cases were similar to those in recognised congenital infections including intrauterine growth retardation, hepatosplenomegaly, conjugated hyperbilirubinaemia, anaemia, and thrombocytopenia. However respiratory distress was a prominent feature and major cause of death with lung histology in five out of nine cases showing congenital pneumonia with intralveolar haemorrhage. In this context it is interesting to note than nine out of the 11 babies who died from pulmonary or gastrointestinal haemorrhage caused by neonatal septicaema were HIV positive. Microcephaly was an unusual feature seen in only two surviving HIV positive cases both of whom were probably infected with rubella.

In order to determine how maternal HIV infection predisposes to septicaemia and congenital infection more sophisticated investigations are needed but are not at present available in Zimbabwe. The polymerase chain reaction could be used to determine what proportion of the deaths are actually infected with the HIV virus,[20] viral culture being more difficult and antigen tests being negative at birth even in infected babies.[21] Total IgM measurements soon after birth could help establish the diagnosis of congenital infection and tests for rubella or cytomegalovirus specific IgM could be used to confirm infection by these viruses.

I am most grateful to Dr N T Chaibva, the medical superintendent of Mpilo Central Hospital, for permission to perform this study, to all the staff of the Maternity Hospital microbiology and histopathology departments for their help, and especially to Sr A M Luza, Sr F M Moyo, Dr J J Valdes Gomez, Dr F J Gonzales de Chaves, Dr Z Sibanda, Dr M K Khan, Dr R M A W El-Gammal, Dr R A Dlodlo, and Mrs H E Aiken for their invaluable assistance.

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Archives of Disease in Childhood 1992; **67**: 600–602

Deaths at home and in hospital in Zimbabwe

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Accepted 18 December 1991

Abstract

A prospective study was done of children less than 13 years of age, who died at home or on their way to hospital and those who died in hospital, over a one year period. Fifty seven (86%) of the 66 children who were dead on arrival and 94 (77%) of the 122 children who died after admission were 2 years old or less. The main causes of death in both groups were identical and infections were the most frequent diagnosis. AIDS was the most common cause with 23 (35%) of the deaths in the children who were dead on arrival and 27 (22%) of the deaths in the children who died after admission. An overall positive HIV-I serology was found in 31 (47%) of the children in the dead on arrival group and in 50 (41%) of the children in the group that died after admission.

Data on childhood mortality outside hospital in developing countries is scanty and most information is obtained from hospital records.[1 2] This paucity of accurate information regarding exact causes of death in children in developing countries prompted us to look into this problem in some detail. It was thought necessary to evaluate prospectively both those children who died at home or *en route* to hospital and those who died after admission.

The Bulawayo Central Hospital serves a mixed population. It is one of the two teaching hospitals in Bulawayo and a referral centre for half of the southern part of the country. It is also a general hospital for the middle class suburbs where a substantial part of the population consists of domestic workers who predominantly use the hospital, while the middle class uses a nearby private hospital. There are two military barracks in the catchment area.

The study was approved by the Medical Research Council of Zimbabwe.

Patients and methods

EXTRAMURAL DEATH

All infants and children, aged from 1 day to 13 years, who were presented dead on arrival at Bulawayo Central Hospital from June 1990 to July 1991 were seen by one of the authors. Information obtained included age, sex, and circumstances of death of the child. A detailed medical history was taken from the parents or caretakers and any treatment given before death was noted. A detailed physical examination was performed and specimens of cerebrospinal fluid, blood, urine, and stool were taken for culture and sensitivity. Blood was also obtained for HIV-I test (enzyme linked immunosorbent assay (ELISA); Abbott Laboratories Enzyme Immunoassay). The time lag between the presumed time of death of the child and the collection of the specimens was within two hours. Previously diagnosed cases of AIDS were not further investigated. A postmortem examination was done with parental consent and in appropriate cases the necropsy was requested by the police. A definitive diagnosis was made on the basis of the history, and the physical and laboratory findings, backed up by the necropsy report. The bereaved relatives were given the opportunity to discuss the child's death and its cause or causes with one of the authors four to six weeks later.

INTRAMURAL DEATH

In order to determine whether the characteristics of the children who were dead on arrival were different from those who died after admission, all children and infants aged from 1 day to 13 years, who died in the hospital's general paediatric wards, were studied prospectively during the same year. Admissions to the paediatric surgical ward and babies admitted to the neonatal ward from the maternity ward of the hospital were excluded from the study. In the period under consideration there were 2038 admissions to the general paediatric wards.

DEFINITIONS

A diagnosis of probable AIDS was made when the child presented with a constellation of at least two of the following features: severe pneumonia, oral candidiasis, generalised lymphadenopathy, hepatosplenomegaly or failure to thrive, backed up by a positive HIV-I serology (ELISA).[3] HIV associated disease was defined as illness without the above mentioned constellation but with a positive HIV-I serology on testing.

Results

Over the one year period, 118 infants and children were certified dead on arrival in the emergency department. There were 15 abandoned newborn babies, 16 children with accidents and 21 children with inadequate data, who were excluded, leaving 66 children for analyses. Forty eight (73%) of these 66 children were infants and 57 (86%) were aged 2 years or less. There were 39 boys and 27 girls. During the same period 122 children died after admission on the general paediatric wards. In this group 69 (57%) were infants and 94 (77%) were aged 2 years or less. There were 54 boys and 68 girls in the admitted group. The figure shows the age distribution of both the children who died outside the hospital and those who died after admission.

CAUSES OF EXTRAMURAL DEATH

Table 1 shows the causes of death in the 66 children who were dead on arrival. The most frequent cause of death was AIDS which was diagnosed in 23 children (35%). Of these, 14 were diagnosed on previous hospitalisation. In the nine previously undiagnosed cases, multiple micro-organisms were isolated on culture of various body fluids (table 2). An overall positive HIV-I serology was found in 31 of the 66 children (47%).

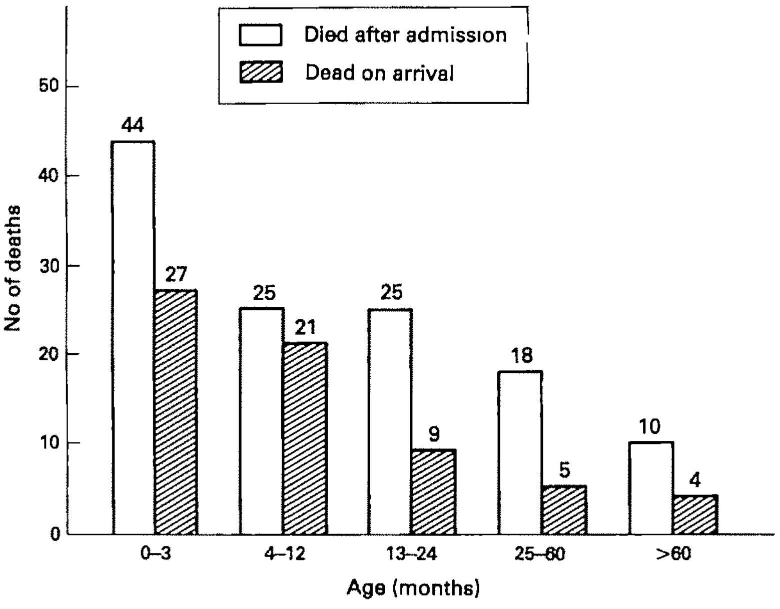
Table 1 Causes of death in 66 fully analysed children who were dead on arrival

Cause	*No (%) of children*
AIDS	23 (35)
Pneumonia (HIV associated, n=7)	12 (18)
Sepsis	6 (9)
Heart disease	4 (6)
Gastroenteritis (HIV associated, n=1)	3 (5)
Malnutrition	2 (3)
Anaemia	2 (3)
Cerebrovascular accident	2 (3)
Prematurity	2 (3)
Aspiration	2 (3)
Miscellaneous:	
Meningitis	1
Congenital syphilis	1
Pulmonary tuberculosis	1
Obstructive uropathy	1
Paraffin ingestion (pneumonitis)	1
Asphyxia	1
Haemorrhagic disease of newborn	1
Anaphylactic shock	1

Table 2 Micro-organisms cultured in nine children with previously undiagnosed AIDS who were dead on arrival

Micro-organisms	*Specimen*	*No of children**
Mycobacterium tuberculosis	Pericardium	5
Escherichia coli	Blood	3
	Pericardium	1
Klebsiella	Blood	2
	CSF	1
	Urine	1
Streptococcus pneumoniae	Percardium	1
Streptococcus D	Pericardium	1
Micrococcus	Blood	1
Staphylococcus epidermidis	Blood	1
Pseudomonas	Blood	1

*Several children had more than one kind of micro-organism CSF=cerebrospinal fluid.



Age distribution of 66 children who were dead on arrival and 122 children who died after admission.

CAUSES OF INTRAMURAL DEATH

In the same period, 2038 children were admitted of whom 122 died, a mortality of 6%. Table 3 shows the causes of death in these children. Twenty seven (22%) children were thought to have died of AIDS. An overall HIV-I seropositivity was found in 50 children (41%).

Table 3 Causes of death in 122 children who died after admission in hospital

Cause	*No (%) of children*
AIDS	27 (22)
Pneumonia (HIV associated, n=16)	26 (21)
Heart disease (HIV associated, n=1)	13 (11)
Sepsis (HIV associated, n=1)	9 (7)
Meningitis (HIV associated, n=2)	9 (7)
Gastroenteritis (HIV associated, n=3)	7 (6)
Malnutrition	5 (4)
Congenital syphilis	4 (3)
Seizures (intractable)	4 (3)
Neoplasma	3 (2)
Neuromuscular disorder	3 (2)
Miscellaneous:	
Biliary atresia	1
Renal failure	1
Prematurity	1
Haemorrhagic disease of the newborn	1
Pharyngeal abscess	1
Diphtheria	1
Kernicterus	1
Uropathy	1
Intoxication	1
Neonatal tetanus	1
Suicide	1
Rabies	1

Comparison between the causes of death in the two groups revealed an essentially similar pattern with the exception of meningitis, which was relatively under-represented in the group of children who were dead on arrival.

Discussion

The study shows that the pattern of deaths of infants and children at home and in hospital are similar. Lack of reporting of the deaths at home causes falsely low hospital mortality rates as many of these children would have probably died anyway even if they managed to be admitted.

As expected, the mortality was highest in the lower age groups with the first two years accounting for 86% and 77% of the deaths in the groups of children who were dead on arrival and died after admission, respectively. Out of the total number of deaths, infants accounted for 73% in the group of children who were dead on arrival and 57% in the group who died after admission. A similar observation was made by Choudhary and Jayaswal in a prospective study on childhood mortality in India.[4] The main causes of death in both of the groups were identical and infections were the most frequent diagnosis (tables 1 and 3). This is in contrast to industrialised countries where congenital anomalies and accidents are the main causes of death in children.[5 6] In a recent retrospective hospital based study from a teaching hospital in Nigeria,[1] measles and protein energy malnutrition proved to be main causes of death in children less than 2 years of age, whereas diarrhoea was the main cause of death in children between 1 and 6 years in a prospective community based survey in India.[4] In neither study, however, were necropsies done and diagnoses were based on clinical criteria or information from the parents which may raise doubts as to the exact causes of death.

In a newsletter, Nkrumah and Nathoo listed seven main causes of childhood death in Zimbabwe which included measles, tetanus and malnutrition, but gave no figures to reflect the order of relevance of these causes.[7] In our series of 188 children there was only one case of neonatal tetanus and one case of diphtheria (table 3). Death from measles was conspicuous by its absence. The obvious lack of a substantial contribution to mortality from childhood diseases preventable by immunisation is remarkable. Although the period of observation is short, deaths from such diseases must now be regarded as rare in our area. Deaths from protein energy malnutrition appears to be showing a similar trend. This observation, however, may have been biased by the fact that our hospital is a referral hospital and therefore cases of malnutrition might have been dealt with in the rural district hospitals. Another remarkable observation is the total absence of cases of cot death (sudden infant death syndrome) among the infants who died at home.

The high prevalence of HIV associated mortality of 47% in the group who were dead on arrival and 41% in the group who died after admission is alarming. The diagnosis of HIV infection in infants by ELISA is problematic because of passive transfer of maternal antibodies, but methods for HIV antigen detection or virus isolation are not available in Zimbabwe. The problem is made worse by the fact that the test can be carried out only once in a deceased person. The clinical presentation with infections associated with HIV-I and a positive ELISA strongly suggests that these children were immunocompromised. In particular, young infants with severe pneumonia and positive serology (HIV associated pneumonia) showed a high mortality in both the groups. It is estimated that recent reductions in child mortality are likely to be reversed in regions where HIV-I infection is prevalent.[8]

In children with AIDS a substantial number have been shown to be infected with *Pneumocystis carinii*, pathogenic bacteria, and *Mycobacterium tuberculosis*.[9] In our series, although small, all nine previously undiagnosed cases of AIDS, who were brought in dead and were fully investigated, were found to be infected with either pathogenic bacteria or mycobacterium. Infection with *P carinii* was not looked for because of lack of appropriate laboratory facilities.

Although our access to medical literature is limited, we recall no previous studies involving children in a developing country, which have dealt with death at home by identifying the causes in a systematic, clinical manner. In many developing countries the causes of death in children are based on interviews with parents and health workers or on postmortem examinations which are often inadequate. These approaches have inherent difficulties and are prone to gross error which can only be overcome by the method of investigation which we have adopted, particularly for those children dying at home. Many hospitals and health centres have no laboratory facilities to verify the clinical impression. In some developing countries deaths at home do not necessarily have to be delivered to hospital, as is compulsory in Zimbabwe, or even reported to the authorities; this is particularly true in rural areas. It is therefore important in discussions of childhood mortality from developing countries to define clearly the population under study and how the cause of death was identified and by whom.

In conclusion, there is a substantial number of children who die at home or on their way to hospital. The causes of death in this group of children are of a similar pattern to the causes of death in the children who were admitted to hospital, where infections, especially AIDS, were the most common diagnosis. There is need for a large scale study of the type undertaken here.

It is hoped that improved primary health care and better education of the parents and health workers can reduce the number of children who die at home.

We would like to thank Dr GS Gwisai, medical superintendent, United Bulawayo Hospitals and Dr F Gonzalez de Chaves, pathologist, and the staff of the accident and emergency department for their support.

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Archives of Disease in Childhood 1992; **67**: 603–607

Intensive enteral feeding in advanced cirrhosis: reversal of malnutrition without precipitation of hepatic encephalopathy

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Abstract

Ten children with advanced cirrhosis and malnutrition ($<90\%$ weight for height) were fed for eight weeks with a nasogastric feed comprising whey protein (enriched with branched chain amino acids), fat as 34% medium chain and 66% long chain triglycerides, and glucose polymer. Six of the children were studied for an eight week control period before feeding. Weight, triceps skinfold thickness, mid-arm circumference, mid-arm muscle area, and fasting plasma ammonia and amino acid concentrations were measured before and after the control period and after the consequent feed period. Results showed that despite high energy and protein intakes the children remained malnourished over the control period. All anthropometric indices improved significantly during the feed period, and no child developed clinical encephalopathy. The feed period was associated with a small, and not clinically significant, increase in the plasma ammonia concentration, but no consistent trend in the plasma amino acid concentrations. Thus, in children with advanced hepatobiliary disease awaiting liver transplantation, enteral feeding improved nutritional status without adverse clinical or biochemical effects.

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Accepted 4 February 1992

Malnutrition is common in children with hepatobiliary disease.[1,2] It may be associated with a number of adverse effects such as decreased brain growth,[3,4] impairment of mental development,[3] and decreased immunocompetence[5] with an increased susceptibility to infection.[6] The pathogenesis of malnutrition in liver disease is poorly understood. Anorexia,[7] increased metabolic rate,[8] and fat malabsorption[9] are all potentially important contributory factors and raise the possibility that reversal of malnutrition may occur with appropriate intensive nutritional support. We have addressed this question with a study of intensive enteral nutrition in a group of children with severe chronic liver disease. Such an intervention in patients with advanced liver disease might be expected to exacerbate already impaired nitrogen tolerance[10] and precipitate hepatic encephalopathy.[11] Moreover, fat malabsorption is well recognised in children with cholestatic liver disease,[12,13] and an increase in dietary lipid might be expected to precipitate diarrhoea. However, there is some evidence that a nitrogen load high in branched chain amino acids may be less likely than a simple high protein diet to exacerbate such abnormalities or to precipitate hepatic coma.[14] Similarly, medium chain triglycerides may be better tolerated than long chain triglycerides in patients with chronic liver disease.[9] We therefore used a modular feed in which the nitrogen source was enriched with branched chain amino acids and the lipid source was a mixture of long and medium chain triglycerides. We performed an open controlled study with two aims. First, to determine whether malnutrition complicating advanced cirrhosis could be reversed by short term intensive enteral feeding lasting eight weeks. Second, to establish whether such an intervention was associated with dangerous clinical or biochemical sequelae.

Details of subjects

Case No	*Diagnosis*	*Age (years)*	*Bilirubin (μmol/l)*	*Albumin (g/l)*
1	Biliary atresia	0·5	140	39
2	Biliary atresia	1·92	70	30
3	Neonatal hepatitis/cirrhosis	0·83	15	25
4	Biliary atresia	0·67	260	31
5	α_1-antitrypsin deficiency	2·42	40	24
6	Biliary atresia	0·83	190	35
7	Neonatal hepatitis/cirrhosis	0·83	190	35
8	Biliary atresia	7·92	30	35
9	Biliary atresia	0·67	250	29
10	α_1-antitrypsin deficiency	0·33	170	43

Subjects and methods

Ten children (median age 9 months, range 4 months to 8 years; six boys and four girls) were studied. All 10 had cirrhosis that had been proved at biopsy. The plasma bilirubin and albumin concentrations at the start of the study and the aetiology are shown in the table. All were less than 90% of their expected weight for height (range 62–88%, median 78%).[15,16] Three had ascites at the start of the study and five had oesophageal varices.

Six of the children were observed over an eight week control period on their own diet before the eight week period on the trial diet. Such a control period was not possible in four children, who presented urgently to hospital and started immediately on enteral feeding.

The study was approved by the local research ethical committee and all parents gave their informed consent.

DIETARY ASSESSMENT

Nutrient intake before enteral feeding was assessed using seven day weighed records by parents and subsequent computer analysis of the dietary records.[17] Recall dietary assessment at home before feeding and dietetic advice given were noted for the other three children.

ENTERAL FEED

A modular feed was used. The nitrogen source (Generaid, Scientific Hospital Supplies) was whey, enriched with free branched chain amino acids (whey protein 73%, and free branched chain amino acids 27%, in protein gram equivalents). The total branched chain amino acid content of the protein was 31% (including branched chain amino acid content of whey). Each child received 4 g/kg/day of protein. Fat, comprising 34% medium chain triglyceride and 66% long chain triglyceride, and carbohydrate (as glucose polymer) were given as Duocal (Scientific Hospital Supplies). Energy content of the feed was 8% protein, 40% fat, and 52% carbohydrate. Vitamin and mineral requirements were provided for children under 1 year old as Paediatric Seravit (Scientific Hospital Supplies) which contains no sodium or potassium, and for those over 1 year old as Code 544 (Scientific Hospital Supplies) which contains no sodium, potassium, calcium, or phosphate. Sodium and potassium were provided as molar solutions and calcium and phosphate as Calcium-Sandoz and Phosphate-Sandoz (Sandoz). All subjects received additional supplements of vitamins A, D, and E. Initial feed volumes were calculated to provide either 140% of the previous energy intake or 140% of recommended energy requirements per kg for age,[18] whichever was greater. The energy density of the feed ranged between 1 and 1·5 kcal/ml depending on the fluid allowance for the child, with a mean osmolality of 400 mosmol/kg.

ADMINISTRATION OF FEED

Feeding was started in hospital and given by continuous nasogastric infusion over 18–22 hours/day. The initial protein content of the feed was the same as the intake during the control period when this information was available or at 1 g/kg/day where not available. Intake was increased by 1 g per kg per day every third day to a maximum of 4 g/kg/day. The carbohydrate and fat components were also increased stepwise until final energy requirements were reached by five days. The children were encouraged to have additional food during the study period but none took a significant amount. The parents were taught to make up the feed, to care for the nasogastric tube (6FG Silk, E Merck), and to control the infusion pump (Kangaroo Pump, Sherwood Medical) before their child was discharged.[19] The feed was given for eight weeks; blood samples were obtained and anthropometric recordings taken at the start and the end of this period. The children were examined for ascites and signs of hepatic encephalopathy at least every two weeks and the nutrient intake per kg body weight maintained throughout the eight week period.

ANTHROPOMETRY

Measurements were carried out by one observer (CPJC) using the same balance scales (weighing to nearest 25 g), non-stretch plastic tape, Holtain skinfold calipers, and Holtain stadiometer. Triceps skinfold thickness was measured half way between the tip of the acromion process and the tip of the olecranon of the relaxed left arm. The upper mid-arm circumference was measured at the same point. The measurements were expressed as standard deviation (SD) scores.[20] The following standards were used: Sann *et al* (1988) for arm anthropometry under 1 year old,[21] Tanner (1973) for weight and length for all ages and triceps skinfold thickness above 1 year old,[15] and Frisancho (1981) for mid-arm circumference and mid-arm muscle area above one year.[22] The mid-arm muscle area was calculated from the mid-arm circumference and the triceps skinfold thickness[23] and expressed as a percentage of the median of the reference population. Measurements were carried out before and after the eight week control period, and again at the end of the subsequent eight week feeding period for six of the 10 children. For the other four children measurements were carried before and after the feeding period.

BIOCHEMISTRY

Venous blood was taken after a four hour fast at the same time as anthropometry. Plasma ammonia concentration was assayed by a continuous flow ion selective electrode system.[24] Plasma for amino acid analysis was deproteinised immediately after collection by the addition of an equal volume of 3% sulphosalicyclic acid. The supernatant was stored at minus 20°C until analysis. Amino acids were measured by ion exchange chromatography using a lithium buffer system and ninhydrin detection (Kontron Chromakon 500). The reference standards used were Brodehl and Gellissen[25] and Scriver and Davies.[26]

STATISTICAL METHODS

The Wilcoxon signed rank test was used to compare the paired results. Comparisons between the feed and control periods entered the analysis as a quadratic time component. The significance of this comparison was assessed using a repeated measures analysis of variance. Raw data was used for this analysis apart from ammonia concentrations where logarithmic transformation was performed.

Results

DIETARY ASSESSMENT

Seven children had dietary assessments before enteral feeding. Energy intakes were 90 to 165% (mean 130%) of the recommended intake per kg for age[18] and protein intakes 2·6 to 5·7 g/kg/day (median 3·4 g/kg/day). Six children had intakes above that recommended by the World Health Organisation, and these were fed 140% of their recorded intake for the feeding period. The other four children received 140% of their recommended energy intake. Before the trial four children were on normal diets, four were taking energy supplements (carbohydrate and medium chain triglycerides), and two were on Pregestimil (Bristol-Myers), one of whom was also on energy supplementation. Nine of the children had dietetic advice to maximise energy intake.

TOLERANCE OF FEEDING

Both the nasogastric tube and the enteral feed were well tolerated with no adverse clinical events. In particular, diarrhoea was not a problem. Regurgitation, which had been present before the trial, was exacerbated in two infants but lessened with feed thickening. If the polyurethane nasogastric tube continued to be displaced frequently by the vomiting it was replaced by a stiffer polyvinylchloride tube (Portex). None of the 10 children developed fluid overload (development or exacerbation of ascites and/or peripheral oedema). Two of the three with ascites before feeding had lost it by the end of the feed period. The modular nature of the feed allowed precise control of fluid and sodium intake, which aided the control of the ascites. There were no episodes of variceal haemorrhage. All 10 children maintained their target intakes throughout the eight week period.

ANTHROPOMETRY

The weight, mid-arm circumference, and mid-arm muscle area before the eight week control period, where available, and before and after the consequent eight week feeding period are shown in fig 1. Malnutrition was severe before feeding, and nine of the children were more than 2 SDs below the reference mean for mid-arm circumference. All children increased their weight, triceps skinfold thickness, mid-arm circumference, and arm muscle area during the feed period and these changes were statistically significant ($p<0{\cdot}005$). Statistically significant improvements over the intervention period compared with the control period were obtained for all measurements (weight $p<0{\cdot}005$; mid-arm circumference, triceps skinfold thickness, and arm muscle area $p<0{\cdot}001$).

BIOCHEMICAL MEASUREMENTS

Individual plasma ammonia concentrations at the start of the eight week control period and before and after the eight week feed period are shown in fig 2. Prefeeding plasma ammonia concentrations in eight out of the 10 children were above the laboratory reference range for well children. Analysis of the changes in ammonia concentration both during the feed period and between the control and feed period were statistically significant ($p<0{\cdot}05$). However, there was much variance in the data and the concentrations never approached those usually associated with clinical problems.[27] No patient developed hepatic encephalopathy, and no parent reported increased drowsiness in their child. Indeed, nine out of the 10 children were reported by parents to have become more active and lively during the trial.

The mean fasting plasma amino acid concentrations before and after feeding are shown in fig 3. Concentrations are expressed as the number of SDs from the reference mean for the age band. The majority of amino acid concentrations were in the normal range before feeding

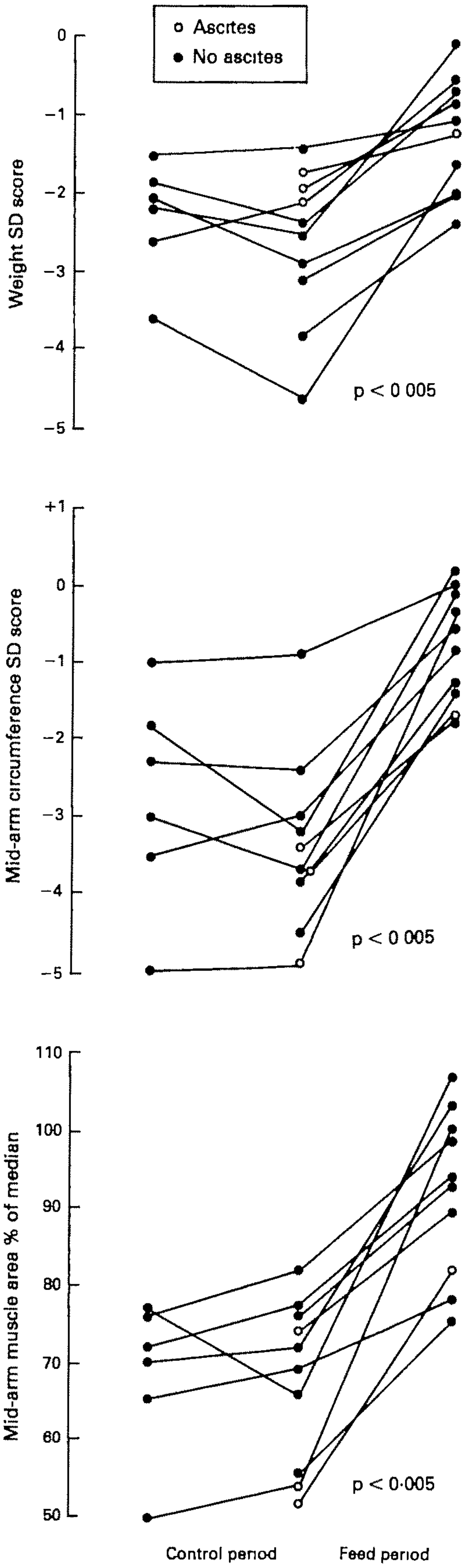

Figure 1 Changes in weight SD scores, mid-arm circumference SD scores, and mid-arm muscle area as % of median (see text for reference population standards) for six children with cirrhosis over the eight week control period and all 10 subjects over the eight week intensive enteral feeding period. Prefeed versus postfeed weight SD score, mid-arm circumference SD score, and mid-arm muscle area all <0·005. Change in parameters over feed period were significantly different from change over control period. weight SD score <0·005, mid-arm circumference SD score, and mid-arm muscle area % of median p<0·001.

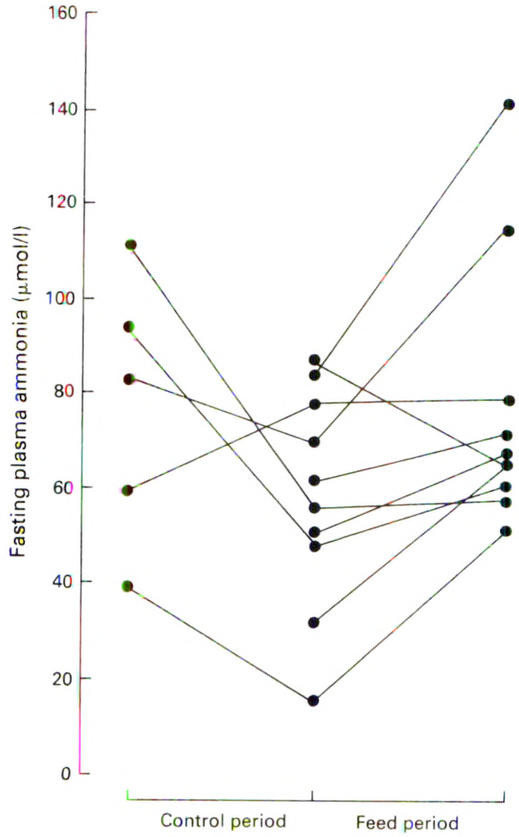

Figure 2 Fasting plasma ammonia concentrations before and after eight week control period and after consequent enteral feeding period in children with cirrhosis. Upper limit of laboratory reference range (95% confidence limits) is 40 μmol/l. Analysis of the paired results before and after the feed period and the change over control period compared with that over the feed period gave $p<0\cdot05$ for both.

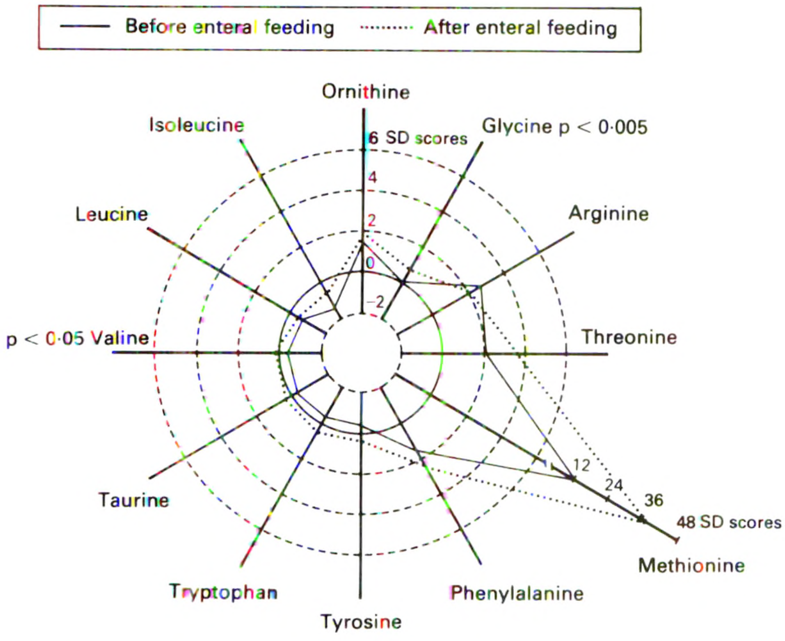

Figure 3 Changes in mean fasting amino acid concentrations of 10 children with cirrhosis before and after eight weeks of enteral feeding expressed as a SD score of reference standards.[25 26] The bold circle represents the mean amino acid concentration for the reference population. The dashed concentric circles represent 2 SD steps from the reference mean. (Methionine has an extended scale.) Individual amino acids values are plotted on the radii of the diagram. Analysis of the individual paired results before and after feeding for the amino acids shown (and also glutamine, aspartate, cystine, serine, alanine, proline, and lysine) were statistically non-significant apart from valine, $p<0\cdot05$ and glycine, $p<0\cdot005$.

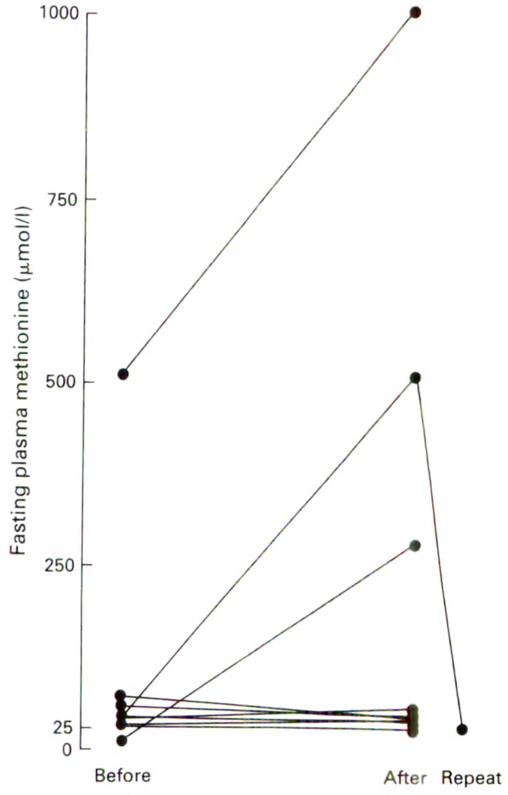

Figure 4 Fasting plasma methionine concentrations for 10 children with cirrhosis before and after the eight week enteral feeding period with a repeat result for an individual (still on the trial regimen) who had an intercurrent viral infection at the time of the eight week sample. Analysis of the paired results was not significant.

(−2 to +2 SD) and were unchanged afterwards. In particular branched chain amino acids were all near the reference mean both before and after feeding. Lysine, threonine, and phenylalanine concentrations were above the reference range initially, but did not increase after feeding. Mean methionine concentrations were raised both before and after feeding, a finding consistent with severe liver disease. While the mean methionine concentration was higher at the end of feed period than before, there was no statistically significant difference between the individual paired results. This rise was biased by the results in three children in whom methionine concentrations increased greatly. Two of those three had deteriorating liver function during the study as determined by prolongation of prothrombin time. The third child had an intercurrent viral infection in week 8 of the feed period at the time of the second sample, and a repeat methionine concentration after recovery while still on nasogastric feeding was similar to the prefeed value (fig 4). The other seven children had appreciably raised methionine concentrations up to 9 SDs above the reference mean both before and after feeding with little individual change.

Discussion

Intensive enteral feeding appreciably improved the nutritional status of the children, assessed clinically by upper arm measurements and by weight. There were no serious deleterious effects. In particular, no episodes of hepatic encephalopathy were precipitated. Although the children studied were malnourished, we found no evidence of a poor dietary intake. This differs from the observations of Watkins and Glassman.[7] The majority of children we studied had received dietary advice aimed at increasing energy intake before feeding and had an energy intake higher than that recommended for age and weight.[18] Our sample was small but these observations point to malabsorption, poor utilisation, or increased metabolic requirements as more important mechanisms for protein energy malnutrition than inadequate intake. This is supported by the demonstration of Pierro *et al* that children with extrahepatic biliary atresia have both an increased resting energy expenditure and large energy losses in the stools.[8]

Fasting plasma ammonia concentrations were above the reference range before feeding and had risen further by the end of the study period. However, this was not associated with any clinical deterioration and the concentrations were much lower than seen for example in Reye's syndrome.[28] This study had small patient numbers and until more data and clinical follow up are available, we would advise clinical observation for adverse effects and measuring plasma ammonia in situations where dietary nitrogen is being increased in children with severe liver disease.

The amino acid profiles before feeding showed similar abnormalities to those documented previously,[10] with particular elevations of methionine, threonine, and phenylalanine. Branched chain amino acid concentrations were in the reference range. This pattern changed little with enteral feeding and there were no increases in branched chain amino acid concentrations. Thus, in the group studied, no gross abnormality was attributable to the high nitrogen load. In this study we have demonstrated that malnutrition in children with cirrhosis occurs despite a normal or high energy intake; it can be reversed without deleterious effects by an intensive period of enteral feeding. However, we cannot conclude that branched chain amino acid enrichment has any advantage over standard protein and this will require further study.

The only chance of long term survival for these children is liver transplantation. We speculate that better nourished children will have improved survival before transplantation during their wait for a donor organ. In one centre, 25% of children died while awaiting transplantation.[29] Poor pretransplant nutrition may also be associated with an adverse result after grafting.[30] Prior correction of severe protein energy malnutrition may therefore improve the long term outlook of children with severe liver disease awaiting transplantation.

We thank Alan Girling, School of Mathematics and Statistics, University of Birmingham, for statistical advice; Scientific Hospital Supplies, Liverpool for supply of the feed components; and 'Remember Rebecca Trust' for provision of computer equipment.

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Archives of Disease in Childhood 1992; 67: 608–612

Using the steatocrit to determine optimal fat content in modular feeds

M O Rawashdeh, D R Lloyd, J W L Puntis, G A Brown,* I W Booth

Abstract

The steatocrit was measured in infants with protracted diarrhoea who were receiving intragastric modular feeds. Measurements were made when fat intake was constant to determine steatocrit variability and during increases in fat intake to determine fat tolerance limits. Steatocrit variability was expressed as the range between a subject's lowest and highest steatocrit value. The median between-stool and between-day variabilities were 2% and 11% respectively.

Variability was also measured in seven healthy breast fed infants. In the five still displaying appreciable physiological steatorrhoea, the between-day variability (median 8%) and between-stool variability (median 9%) were not significantly different from the protracted diarrhoea group.

In the fat tolerance investigations in the protracted diarrhoea group, the steatocrit increased with increases in the module fat content. Fat intake and steatocrit were significantly positively related. A significant negative correlation was seen between steatocrit and weight gain, the latter becoming negligible at steatocrit values around 30%.

Modular feeds have an important role in the management of infants with severe, protracted diarrhoea. Each macronutrient can be varied independently, both quantitatively and qualitatively, so that modular feeding often obviates the need for parenteral nutrition.[1] For example, in infants unable to tolerate the glucose polymer concentration present in protein hydrolysate based feeds, an isocaloric quantity of carbohydrate can be provided in a modular feed as a mixture of glucose polymer and sucrose without exceeding the carbohydrate tolerance limit.

Tolerance limits for carbohydrate can be established readily by monitoring stools for the first appearance of excess sugar using the Clinitest tablet test (Ames Laboratories) of Kerry and Anderson.[2] Fat is a more energy dense and therefore more effective energy source and there is evidence to suggest that it is better tolerated than carbohydrate during protracted diarrhoea.[3] However, fat intolerance, unlike carbohydrate intolerance, is not necessarily marked by a dramatic increase in stool volume or other clinical signs and steatorrhoea may have important adverse effects.[4] There is therefore a need for a rapid and simple test for stool fat content, analogous to the Clinitest for carbohydrate, for use in patients receiving modular feeds.

Phuapradit *et al*, measuring fat excretion in the newborn, showed a significant positive correlation between the stool fat concentration determined chemically and by a simple, rapid microvolumetric measurement which they named the steatocrit.[5] In the steatocrit, the stool fat content is determined by measuring the thickness of the fat layer produced by centrifugation of a stool and water homogenate and expressing it as a percentage of the total non-aqueous phase (fat plus stool solids layers). The effect of the variable stool water content is therefore eliminated.

The procedure was validated by showing a significant positive correlation between the steatocrit value and the stool fat content determined chemically.[5] Other workers showed a positive correlation between the steatocrit value and the fat content of a three day stool collection but used the same stool homogenate for both analyses.[6] The correlation between the fat content of a stool collection (72 hours or longer) and a single random stool steatocrit measured during the collection period has not been determined and there is very little information available on between-stool variation of the steatocrit and none on between-day variation. The clinical value of the single random stool steatocrit therefore remains unknown.

In this study the steatocrit has been evaluated for a specific role which did not require previous validation of the relation between the fat content of a sample from a single stool and the fat content of several days' stool collection. We have used it to determine the fat intake optimum for infants with protracted diarrhoea who were receiving modular feeds by continuous intragastric infusion. We have also determined the between-stool and between-day variability of the steatocrit and compared the results with steatocrit variability in a group of normal neonates.

Subjects and methods

INFANTS RECEIVING MODULAR FEEDS

Steatocrit values were determined in a group of 14 infants with protracted diarrhoea aged 1–9 months (median 4 months). Nine had post-gastroenteritis syndrome, four were recovering from necrotising enterocolitis, and one had cystic fibrosis. All were in hospital receiving modular feeds by continuous nasogastric infusion. Body weights were measured daily.

NORMAL INFANTS

Steatocrit values were determined in a group of

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Accepted 7 January 1992

Reprints not available.

*Sadly, Mr Geoff Brown died on 12 February 1992.

seven healthy infants, aged 12–63 days, who were at home and exclusively breast fed. Babies of this age were selected because they had steatorrhoea without the potential complications of gastrointestinal pathology.[7]

MODULAR FEEDS

The 14 infants with protracted diarrhoea were fed by continuous intragastric infusion of a modular feed in which protein was provided as comminuted chicken (Cow and Gate) 30 g/100 ml, carbohydrate as a variable mixture of sucrose and glucose polymer (Maxijul, Scientific Hospital Supplies), and fat as an arachis oil emulsion (Calogen, Scientific Hospital Supplies). The module carbohydrate content (10 g/100 ml) was constant throughout for all subjects and none had evidence of carbohydrate malabsorption at any time.

STOOL COLLECTION REGIMEN

Between-stool variability was determined in 11 of the 14 infants with protracted diarrhoea by sampling all stools passed over a single 24 hour period. Between-day variability was determined in nine of the group by collecting stool samples once daily for at least three consecutive days. The variability studies were conducted when fat administration was at a constant daily value. The fat intake-steatocrit relationship was determined during periods of daily incrementation of the module fat content.

In the healthy infants, all stools were sampled over 72 hours. Between-stool variability was assessed using stools from the day which produced the most stool specimens. Between-day variability was assessed using the first stool collected on each of the three days.

STEATOCRIT PROCEDURE

The method of Phuapradit *et al* was used with the following modifications.[5] The stool homogenate concentration was reduced to a stool: water ratio of 1:3 w/w and homogenates were prepared using a Potter-Elvehjem glass and Teflon homogeniser (0·15 mm clearance) instead of the pestle and mortar with sand procedure originally described. A lipid stain (rhodamine 6G) was added to the stool homogenate for improved demarcation of the fat-aqueous and solid-aqueous phase boundaries after centrifugation. Fat and solid phase thickness was measured with a dial caliper calibrated to 0·1 mm.

In some stool samples the quantity and nature of the lipid present resulted in the separation of a 'waxy' lipid material, during homogenisation, which adhered to the homogeniser surfaces leading potentially to an under estimation of fat content. Heating the stool-water mixture briefly to 70°C in a water bath before homogenisation dispersed the adherent lipid and the heating step was used therefore for all stool samples in the study. In a validation experiment in which steatocrit values were determined in five waxy stools and 36 non-waxy stools, with and without the heating step, steatocrit values were significantly increased ($p<0·05$) in the waxy stools after heating but not in the non-waxy samples.

STEATOCRIT METHOD IMPRECISION

Imprecision was determined by separate batch, duplicate analysis of 16 stools. The stools were included in four batches analysed over a period of seven days. The 16 duplicate mean steatocrit values covered the range 7–58%. The coefficient of variation was 17·2%. The range of differences between the 16 duplicate analyses was 0–23%, median difference 3%.

The coefficient of variation produced by homogenising 16 samples taken from the same stool was 13·1%. The median steatocrit value for the 16 replicate analyses was 16%, range 13–20%.

STEATOCRIT VARIABILITY

Steatocrit variability was expressed as the difference between the highest and lowest steatocrit value produced by a baby in the interval of interest. If, for example, the lowest and highest values were 2% and 19% respectively, then variability was recorded as 17%.

STATISTICAL EVALUATION

All statistical evaluations were non-parametric. The degree of association between two measurements and significance was determined using the Spearman rank correlation coefficient. The Mann-Whitney U test and Wilcoxon matched pairs signed rank test were used to determine the significance of differences between unpaired and paired data groups respectively.

Results

INFANTS WITH PROTRACTED DIARRHOEA

The between-stool steatocrit variation is shown in fig 1A. In 11 infants on a constant fat intake, from whom all stools were sampled within a 24 hour period, the highest variability value was 14% (44–58%) and the median value for the group was 2%.

The between-day variation is shown in fig 2. In nine infants in whom stool samples were collected once daily for 3–5 days while on a constant fat intake, the highest variability value was 21% and the median value was 11%.

The relation between steatocrit value and fat intake in the fat tolerance investigations is shown in fig 3. In the 11 infants investigated during periods of daily increases in modular fat content, the steatocrit values increased within 24 hours after each fat increment except in three infants where there was a threshold phenomenon, the steatocrit values increasing only after several increments in fat intake. The positive correlation between fat intake and steatocrit values, using the group pooled data, was statistically significant ($r=0·54$, $p<0·01$).

Using data derived from all 14 babies, there was a significant negative correlation ($r=-0·71$, $p<0·01$) between the mean daily body weight increment (g/kg body weight/100 kcal/day) and a mean steatocrit value derived from seven daily

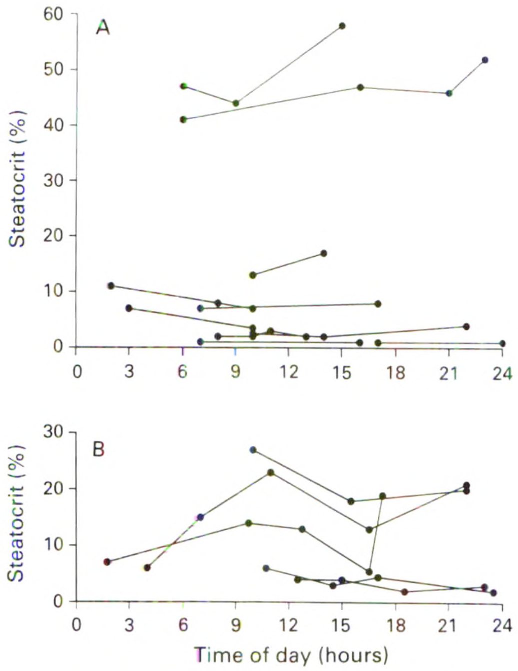

Figure 1 Between-stool variability of the steatocrit in (A) 11 infants with protracted diarrhoea and (B) in five healthy, breast fed neonates. Samples were collected from consecutive stools passed on the same day. Each line joins observations from a single subject.

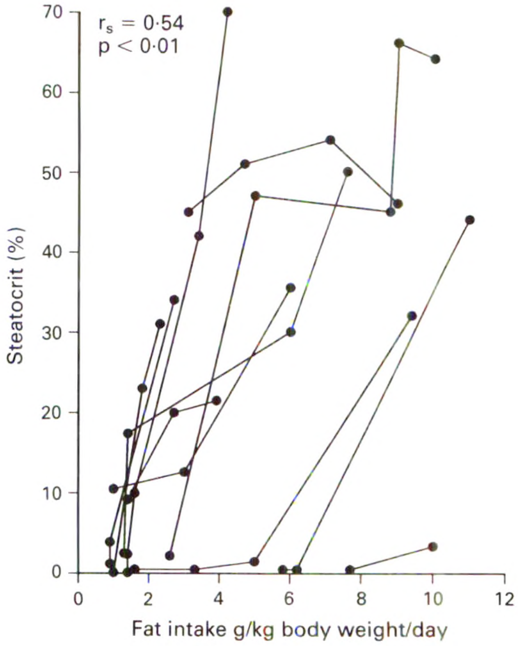

Figure 3 Steatocrit values determined in 11 infants with protracted diarrhoea during progressive daily increases of the module feed fat content. Each line joins observations from a single subject. Spearman rank correlation of the pooled data produced a coefficient of 0·54, p<0·01.

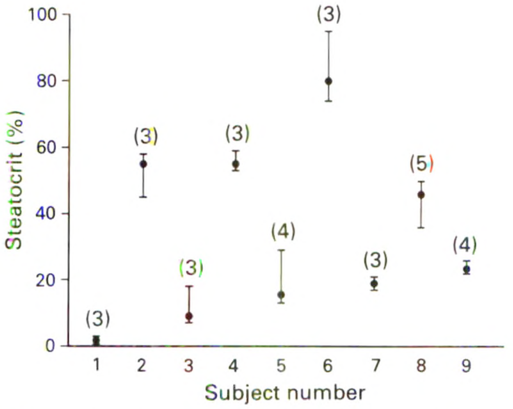

Figure 2 Between-day variability of the steatocrit in nine infants with protracted diarrhoea. Stools were sampled once daily for 3–5 days (number in parenthesis). The vertical plots show the range and median value for the individual infant.

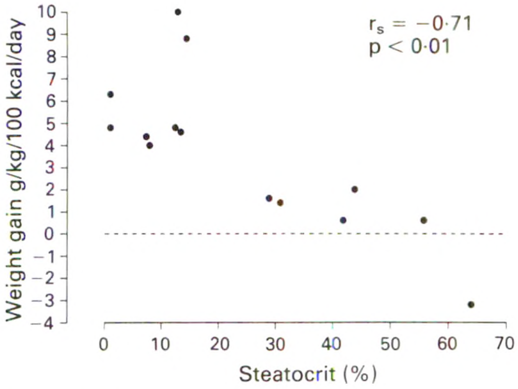

Figure 4 The steatocrit and weight gain relation in 14 infants with protracted diarrhoea. Spearman rank correlation produced a coefficient of 0·71, p<0·01 (100 kcal=418 kJ).

observations, while on a constant fat intake (fig 4). The baby with the highest mean steatocrit value actually lost weight during the study period.

NORMAL INFANTS

The number of stools collected over the 72 hour collection period in each baby varied between 4 and 14 (median 12), the larger numbers being collected from the younger babies. The overall range of steatocrit values in the 71 stool samples was 0–26% and the highest single day, between-stool variability of 17% (6–23%) was seen in the youngest baby (fig 1B). The higher steatocrit values were seen in the younger babies and there was a significant negative correlation (fig 5) between the individual baby's 72 hour median steatocrit value and age (r=−0·893, p=0·01).

Steatocrit values were 2% or less in the oldest two babies aged 6 and 9 weeks. Between-stool variability in the other five babies, who were less than one month of age, was 2–17% with a median of 9%. Their between-day variability range was 2–15%, median 18%.

The between-stool and between-day steatocrit variabilities were not significantly different either within the two groups or between the two groups.

Discussion

Some measure of faecal fat excretion is essential for the objective assessment of fat digestion and absorption. Where the assessment is required at frequent intervals, the chemical methods for determining stool fat content are too cumbersome and a simple, rapid alternative is required. The steatocrit fulfils this need and is technically

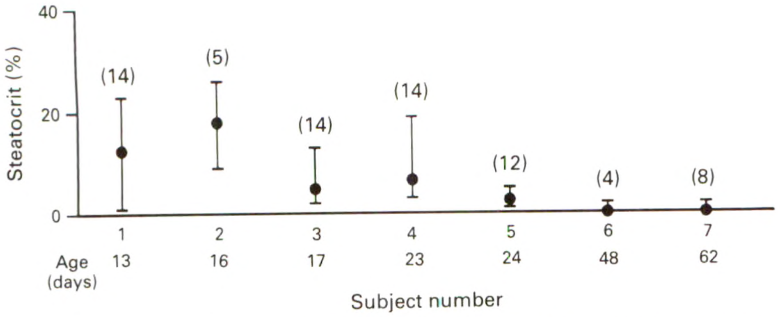

Figure 5 Between-stool variability of the steatocrit in 7 healthy, breast fed infants shown in age order. Samples were collected from stools passed over a 72 hour period. The vertical lines show the range and median value for each infant. The median values showed a significant negative correlation with age. Numbers of parentheses indicate number of stools passed during the 72 hour collection.

satisfactory for infant stools with the modifications described. It has the further important advantage of requiring only a small quantity of stool so that offence is less likely in or out of the laboratory and the problems associated with the collection, storage, and processing of large volumes of stool are eliminated. The problems of containment and disposal of potentially hazardous material are also considerably reduced.

In the healthy infants, the range of values found was almost identical to that found in 5 day old neonates by Phuapradit *et al*[5] and in a recent study in 7 day old neonates.[8] It is unlikely therefore that the method modifications introduced in our study have resulted in any change in values found other than an increase to more accurate values in occasional stools after the heating procedure. The problem of the 'waxy' stool may not be obvious when Phuapradit's sand and mortar homogenisation is used.[5] No other workers refer to it directly but one group 'encountered considerable technical difficulties with this method'.[9]

The decline in steatocrit values with increasing age in the normal babies was consistent with the physiological steatorrhoea of the newborn.[7] The decrease of all steatocrit values to 2% or less by 6 weeks of age was similar to the findings of Iacono *et al* in a larger group of exclusively breast fed neonates.[8]

The highest between-stool variability was seen in the youngest normal babies, with steatocrits ranging from almost zero to values consistent with steatorrhoea. They were bolus fed however and the milk fat content would not have been constant, breast milk secreted in the evening having a 50% higher fat content than milk secreted in the morning.[10] Both factors may predispose to greater between-stool variation.

In the babies with protracted diarrhoea with a constant and continuous fat intake, the between-stool steatocrit variability tended to be smaller and was sufficiently stable for satisfactory determination of their fat tolerance limits.

Other workers have investigated the variability of the steatocrit. Iacono *et al* reported a mean between-stool coefficient of variation of 22·3% in 15 normal infants.[8] The coefficient of variation however was determined for each baby using data from as few as two stools with consequent loss of validity.

The variability found in most of the infants was sufficient to suggest that a single random stool steatocrit determination would not be sufficient for a precise index of steatorrhoea. The mean of several separate stool measurements would be necessary. The between-stool and between-day variability were not significantly different in either group of babies and an index of fat excretion could therefore be produced by sampling stools over any convenient interval which produced sufficient stools.

The rapidity of response to the increases in dietary fat intake, which was consistent with data on mouth to anus transit times in infants,[11] shows the importance of careful control and constancy of fat intake if the steatocrit is used for screening for steatorrhoea. It is also important to ensure that an adequate fat intake is maintained during the stool sampling period.

In our particular clinical context, single steatocrit values proved to be sufficient. The rapid response and close relation to increases in dietary fat provided the information necessary to determine fat tolerance, that is, the point at which further increases in modular fat content provoked a sharp increase in steatocrit value.

In three infants, the fat intake and coincident steatocrit were less closely related than in the rest of the group due to a threshold phase in their fat intake-steatocrit correlation. The steatocrit did not rise sharply after the initial increases in module fat content and their steatocrit values were lower than the rest of the group for a given fat intake. This threshold pattern of response to increasing fat intake has been demonstrated in healthy adults.[12] The inflection in the correlation presumably indicates the fat tolerance limit, that is, the point at which the fat load saturates the digestion-absorption mechanisms. However, even above this inflection point, fat absorption was more efficient than in the remainder of the group, the increase in steatocrit being smaller for a given increase in fat intake. The fat intake:steatocrit regression factor therefore may be an index of the severity of malabsorption or its underlying pathology, the higher the factor the more severe the malabsorption.

A further function of the steatocrit that emerged from the study was its predictive value with respect to weight gain, high values being associated with low weight gains irrespective of the underlying pathology. The slope of this relationship suggested that further increments of fat intake were of limited nutritional value when the steatocrit was 30% or greater. In the context of this study, this correlation also obviates the need to validate the steatocrit by showing a positive correlation with a reference chemical procedure for stool fat measurement, on a 72 hour stool collection for example. If steatocrit measurements have already shown a statistically significant correlation with weight gain (an objective measurement indicative of patient welfare) there is no longer a need to relate it to other fat measurement methods, the relevance to weight gain being a more fundamental relationship in the management of children with protracted diarrhoea.

The steatocrit literature contains very little satisfactory validation or error data for comparison with our modified procedure. Phuapradit *et al* determined method imprecision by repeated analysis of the same two stool homogenates, of high and low steatocrit value, producing coefficients of variation of 2% and 12% respectively.[5] The error associated with homogenate production and any non-homogeneity of stool sample was therefore not included in the assessment.

In a further validation experiment, coefficients of variation of 4·5–15·7%, for steatocrit levels of 5–35%, were found in normal stool samples to which varying quantities of butter had been added to stimulate steatorrhoea.[8] Our coefficient of variation, determined from between-batch duplicate differences in stool samples with a wide range of steatocrit values (7–58%), was a little higher (17·2%) but incorporated the error of the complete procedure over a greater range of steatocrit values.

The relation of steatocrit value and the nature of the stool lipid is so far uninvestigated. The type of fatty acid present in stools during steatorrhoea reflects the dietary fatty acid and will be variable, particularly if therapeutic diets are taken into account. Unsaturated and medium chain fatty acids are liquid at ambient temperatures. Where diets contain large quantities of either lipid any non-absorbed fatty acids in stool should separate more efficiently, when centrifuged for steatocrit measurement, than saturated fatty acids, the predominant dietary fatty acids, which are solid at room temperature. Medium chain fatty acids however would be unlikley to appear in stools in appreciable quantities, the rationale for their use being ready absorption in circumstances where the digestion and absorption of long chain triglyceride has failed.

The statistically significant correlations that have been demonstrated between steatocrit value and stool fat content, measured by gravimetric[5] or chemical analysis,[6] in large subject groups, suggest that any effect of variation in dietary lipid quality is insufficient to obscure the correlation.

With thanks to Gregory Gale and Fraser Brown who participated without complaint in the normal infant group.

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† Iron supplementation should therefore be considered from around 6 weeks.

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Electrogastrography in non-ulcer dyspepsia

S Cucchiara, G Riezzo, R Minella, F Pezzolla, I Giorgio, S Auricchio

Abstract

Fasting and fed gastric electrical activity was recorded by cutaneous electrodes (electrogastrography) in 14 children with unexplained recurrent symptoms of upper intestinal dysfunction, and in 10 controls. The unexplained symptoms included vomiting, epigastric pain, fullness, and early satiety. Mean (SD) age was 7·0 (3) and 7·5 (2) years, respectively. Gastric emptying time of a solid-liquid meal was also measured by real time ultrasonography in all subjects (patients and controls). In all patients radiography and endoscopy excluded structural and focal abnormalities of the gastrointestinal tract. Gastric emptying time was significantly more prolonged in patients than in controls. It was also found that there were appreciable irregularities of gastric electrical rhythm (tachygastria, bradygastria, flat line pattern, and mixed arrhythmia) in 12 fasting and 10 fed patients, whereas controls showed short and rare episodes of arrhythmia during both fasting and fed recording periods. The percentage distribution of the total electrogastrographic energy power across three frequency bands of electrical activity (low, normal, and high) showed that patients were different from controls both for reduced activity of normal frequency and for increased incidence of high and low abnormal frequencies. It is concluded that gastric electrical abnormalities are found in a high proportion of children with recurrent unexplained upper gastrointestinal symptoms. Electrogastrography can be a valuable tool in the assessment of these patients.

Chronic or recurrent symptoms suggesting functional upper gastrointestinal disorders, such as postprandial vomiting, regurgitation, belching, bloating, fullness, epigastric pain, early satiety, and pyrosis, are a frequent cause for referring children to paediatricians. This constellation of symptoms, in the absence of structural abnormalities and focal mucosal lesions of the gut, is known as functional or non-ulcer dyspepsia.[1–3]

Recently, both evidence of abnormal gastrointestinal motor patterns and the beneficial effects of prokinetic drugs on some patients with non-ulcer dyspepsia suggest that the syndrome might be due to disordered gastroduodenal motility.[4–6] It is also worth noting that a number of reports have described abnormalities in gastric electrical activity in patients with unexplained dyspeptic symptoms and delayed gastric emptying.[7 8] This is not surprising as gastrointestinal phasic mechanical contractions are preceded by changes in the electrical activity of smooth muscle cells.

The aim of this study was to measure both fasting and fed gastric myoelectrical activity and gastric empyting time in children with unexplained dyspeptic symptoms. Gastric myoelectrical activity was recorded with electrogastrography, a non-invasive method, by means of cutaneous electrodes attached to the epigastric skin.

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Accepted 17 December 1991

Subjects and methods

SUBJECTS

A total of 24 subjects participated in the study: 14 children had symptoms of non-ulcer dyspepsia and 10 were clinically asymptomatic. Mean (SD) age was 7·0 (3) and 7·5 (2) years, respectively. Postprandial vomiting (n=12) was the most common symptom and it occurred both within (early) and after (late) 30 minutes from feeding and was often preceded by epigastric pain (n=8) or distension (n=6). Other presenting complaints were regurgitation (n=5), pain located in the upper or central region of the abdomen unrelated to vomiting (n=10), fullness (n=6), anorexia or early satiety (n=9), and belching (n=6). In five children a weight:height ratio below the 5th centile was detected.

In all patients upper gastrointestinal radiography excluded structural abnormalities of the gut, and furthermore endoscopy did not reveal focal mucosal lesions (that is, oesophagitis, peptic ulcer disease). Infectious, metabolic, and neurological diseases were also excluded. In five children 24 hour intraoesophageal pH monitoring revealed an abnormal oesophageal acid exposure; normal degrees of this variable have been previously reported.[9]

GASTRIC EMPTYING TIME MEASUREMENT

All subjects (patients and controls) underwent measurement of gastric emptying time by real time ultrasonography performed with a high resolution real time scanner having a 3·5 MHz linear array transducer, applied with minimal abdominal compression. Ultrasonographic determinations were carried out by an operator who was unaware of both clinical condition and diagnosis of the subjects. After an overnight fast children were examined sitting at 45° to the horizontal plane of the examination couch in the fasting state and after eating a 1·25 MJ (300 kcal) solid-liquid meal (bread, butter, ham, fruit juice). The emptying time was determined by measuring every 15 minutes changes in the cross sectional area of the gatric antrum, calculated by measuring the longitudinal and anteroposterior diameters at the level of a sagittal plane passing through the superior mesenteric vein.[10] Final gastric emptying time was considered when the section area had the same value as during the fasting state and no food particles were detected in the antral region; furthermore, it was related to the start of the meal.

ELECTROGASTROGRAPHY

Electrogastrography was recorded by three pairs of cutaneous electrodes (Red Dot 225 3M Co) positioned on the epigastric skin along the axis of the distal stomach that was previously localised by ultrasound. The electrodes were connected to a rectilinear polygraph (R 611, SensorMedics) through nystagmus couplers (9859, SensorMedics). The low and high frequency cut offs were set at 0·016 Hz (time constant 10 seconds) and 0·30 Hz, respectively. Because of interindividual anatomical variations, various recording leads were used and the lead with the best signal to noise ratio was selected for analysis. The electrogastrography signal was simultaneously recorded on the polygraph and on a FM tape recorder. This was later digitised (real time sampling frequency 1 Hz) and fed into a computer for spectral analysis, that is, a method by which the wave form data is decomposed into various frequency components and the relative contribution of a given frequency band to the entire signal is called the 'power' of that frequency band. For example, fig 1 shows a frequency analysis of a signal in a fasting control subject. This analysis has the greatest contribution of its frequencies in the range of 2·5–3·5 cycles per minute (cpm) (that is the normal frequency of gastric electrical signal in humans) and thus has highest 'power' at that frequency range. The percentage power distribution was defined as the ratio between power within one of the three major frequency ranges (1–2, 2·5–3·5, and 4–9 cpm) and total power in all three bands. Spectral analyses were represented by pseudo three dimensional plots, where electrical frequency (0–14 cpm) were plotted on the horizontal axis and time (in 64 second intervals) on the vertical axis. Spectra were obtained as follows: every 64 seconds a power spectrum was computed from the preceding 256 seconds of the electrogastrographic time signal.[11] This procedure generates a series of overlapping spectra and makes both frequency and time analysis possible. The electrogastrography recordings were performed for one hour during a fasting period and for one hour after feeding the same meal that was given during ultrasound measurement of gastric emptying time. Children were examined in a supine position after an overnight fast.

Table 1 Electrogastrographic data for children with non-ulcer dyspepsia and controls. Number (and mean duration in minutes) of arrhythmic episodes

	Tachygastria		*Bradygastria*		*Flat line*		*Mixed arrhythmias*	
	Fasting	*Fed*	*Fasting*	*Fed*	*Fasting*	*Fed*	*Fasting*	*Fed*
Patients								
1			3 (4·6)				1 (5)	
2				6 (5)		2 (5)		
3	2 (5·5)						2 (4·5)	
4	1 (6)				1 (5)			
5		2 (4·5)	2 (4·5)	1 (3)	2 (6)			1 (4)
6			3 (4·6)	5 (4·6)		2 (6·5)		1 (2)
7	3 (5·3)	1 (3)					1 (3)	1 (14)
8								
9		1 (3)	4 (5)	1 (3)	1 (4)	1 (3)	1 (5)	
10			4 (5·3)	5 (6)	1 (3)	2 (4·5)		
11		1 (4)	3 (5·3)		1 (7)			1 (5)
12		1 (8)	3 (7)	1 (4)			1 (3)	1 (3)
13	3 (6·6)	1 (3)		1 (5)	1 (4)		1 (6)	
14	1 (6)	1 (4)		1 (5)				
Controls								
1				1 (1·3)	1 (1)			
2				1 (1)				
3			1 (2)				1 (2)	
4			1 (1)					
5							1 (1)	
6		1 (1·3)						1 (2)
7		1 (2)						
8								
9						1 (1)	1 (1)	1 (2)
10				1 (1)				

Table 2 Distribution of electrogastrography power (%) (median values and ranges) for three frequency bands in children with non-ulcer dyspepsia and in controls

	Frequency band (cpm)		
	1–2	*2·5–3·5*	*4–9*
Fasting:			
Non-ulcer dyspepsia	30·8** (13·3–67·1)	33·4** (13·0–64·1)	27·4* (14·0–47·1)
Controls	17·0 (15·2–31·8)	65·7 (39·3–72·6)	18·7 (13·0–35·4)
Fed:			
Non-ulcer dyspepsia	28·0* (3·8–72·1)	31·5* (15·8–82·5)	29·0 (5·5–50·2)
Controls	15·0 (3·5–25·3)	70·4 (53·7–90·9)	16·1 (4·5–27·3)

*$p<0{\cdot}05$ and **$p<0{\cdot}01$ patients *v* controls.

A frequency included between 2·5 and 3·5 cpm was considered normal. Tachygastria was defined as a frequency between 5 and 9 cpm. Frequencies slower than 2·5 cpm were considered as bradygastria, periods of absent electrical signal were defined as 'flat line pattern', and an irregular rhythm resulting from a combination of both tachygastria and bradygastria was defined as 'mixed arrhythmia'. Arrhythmic periods were taken into account if they lasted $\geqslant 2$ minutes. An arrhythmic index, that is the percentage of arrhythmic time during the time of evaluation, was calculated (60 minutes fasting and 60 minutes postprandially).

Comparison of data between groups was made using non-parametric tests and the level of significance taken was 0·05. Values were given as median and ranges. The study was approved by the ethical committee of our faculty and parents gave informed written consent.

Results

Mean (SD) gastric emptying time (minutes) was significantly prolonged in dyspeptic patients compared with controls (182·14 (35·3) *v* 102·1 (11·2), $p<0{\cdot}01$). In all controls, a gastric electrical activity of about 3 cpm was clearly evident both in the fasting and postprandial states (fig 1 A, B). The difference between patients and controls for arrhythmic index was appreciably significant both in the fasting state (patients: 33·3 (range 10·0–48·3) and controls: 1·6 (range 1·6–33·3), $p<0{\cdot}01$) and in the fed period (patients: 15·0 (range 11·6–66·6) and controls: 2·7 (range 1·6–5·5), $p<0{\cdot}01$). Twelve

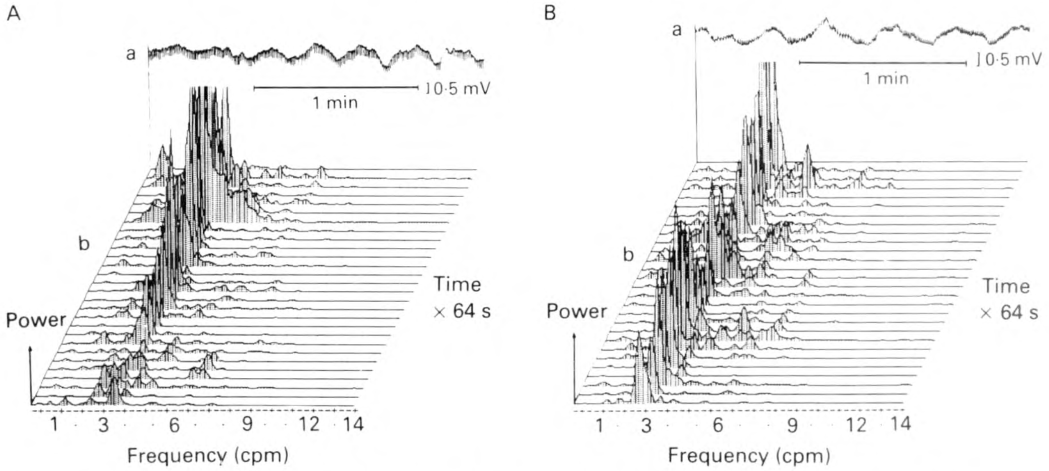

Figure 1(A) Example of electrogastrography tracing (a) and running spectral analysis (b) from a fasting control subject showing a normal 3 cpm activity. In this and the following figures the running spectral analysis represents consecutive segments of electrogastrography data, of which each is overlapped with the preceding segments. Thus, each line represents 64 seconds of new data added to the previous 192 seconds for a total of 256 seconds of electrogastrography data per line. (B) Postprandial recording from a control subject. The electrogastrography tracing (a) and running spectral analysis (b) show a normal 3 cpm activity.

and 10 patients exhibited gastric arrhythmias during fasting and the postprandial period, respectively (figs 2 and 3). The number of fasting and fed arrhythmic episodes for each patient and for controls are reported in table 1. Table 2 shows the electrogastrography power percentage for three major frequency ranges (1–2, 2·5–3·5, and 4–9 cpm); the fasting and fed normal frequency range was significantly less well represented in the patients compared with controls. Low frequency electrogastrography activity was significantly more represented in patients than in controls during both fasting and fed periods, whereas patients were different from controls for an increased high frequency activity only during fasting periods. A comparison of the total electrogastrography power across the three frequency bands is represented in fig 4. Among four patients with normal fed electrogastrography tracings only one had also a normal tracing in the fasting state, whereas three showed appreciable fasting arrhythmias; one patient with bradygastria after feeding had a regular tracing at baseline. Arrhythmic episodes were coincident with dyspeptic symptoms such as nausea, feeling of fullness, bloating, and belching in seven patients (four in fasting and fed states, two only after feeding, one only in the fasting state).

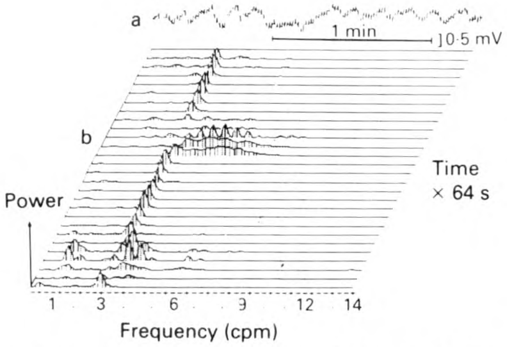

Figure 2 Spectral analysis (b) from a fasting patient with non-ulcer dyspepsia showing an initial regular 3 cpm activity which is followed by a period characterised by absence of 3 cpm activity and a tachygastria pattern at approximately 5–6 cpm peaks. The last part of the spectral analysis shows return of 3 cpm activity. The electrogastrography tracing (a) shows a tachygastria pattern with waves at 5–6 cpm.

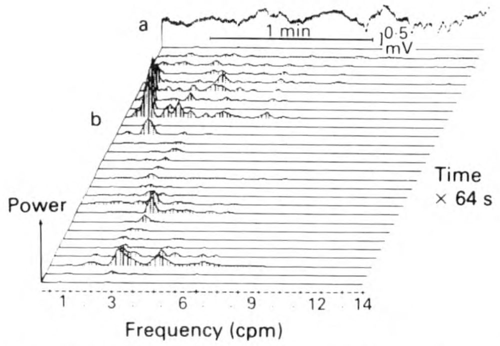

Figure 3 Postprandial spectral analysis (b) from a patient with non-ulcer dyspepsia showing a flat line pattern and periods of low frequency peaks (1 to 2 cpm) (bradygastria). The electrogastrography tracing (a) shows 2 cpm waves.

Discussion

Gastric motor contractions are controlled by electrical activity of smooth muscle cells of the distal two thirds of the stomach; these generate cyclicly recurring depolarisations of cell membrane and are known as slow waves or electrical control activity.[12] In the human stomach, the interval between two consecutive depolarisations is about 20 seconds (frequency 2·5–3·5 cpm). Slow waves originate from a pacemaker area, located in the proximal part of the corpus at the greater curvature, and propagate in the aboral direction. The slow waves, which are constantly present whether contractions occur or not, control frequency and spatial organisation of mechanical contractions of the gut.[13] The latter are usually associated with fast oscillating potential changes, called 'spike potentials' or electrical response activity.

Electrical activity of the stomach can be recorded by electrodes implanted on nasogastric (or orogastric) probes and held by suction against antral mucosa.[14] This technique, however, is rather invasive and detachment of the electrodes from gastric mucosa during prolonged

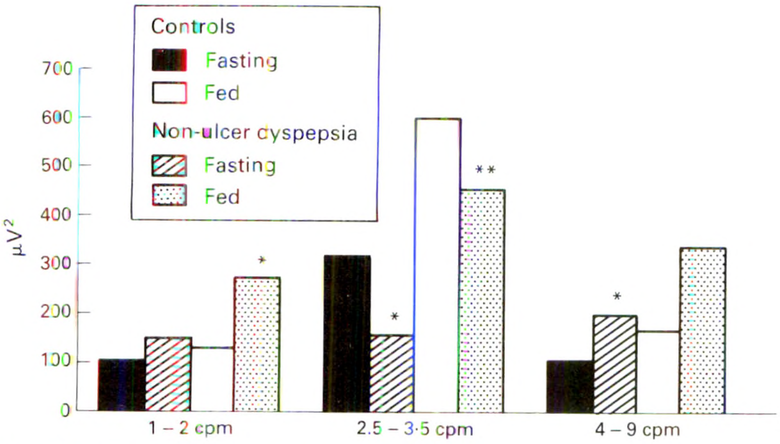

Figure 4 Graphic representation of the total electrogastrography power distribution across three frequency bands of gastric electrical activity. The energy power is reported on the vertical axis as μV^2. *$^*p<0{\cdot}05$ and $^{**}p<0{\cdot}01$ patients v controls.*

recordings occurs frequently.[15] Recent reports have shown that gastric electrical activity can be successfully recorded from surface electrodes positioned over the upper abdominal surface.[16] This technique is known as electrogastrography and has been shown to be reliable in detecting abnormalities of electrical rhythm of the stomach.[17]

Abnormalities of gastric electrical rhythm detected by electrogastrography have been described in normal subjects with motion sickness,[18] in pregnant women with nausea,[19] and in adults with anorexia nervosa.[20] Electrogastrography has been also used in the diagnostic work up of adult patients with unexplained dyspeptic symptoms and various electrical abnormalities have been detected: decreased or absent postprandial increase in electrogastrography amplitude, instability of gastric frequency, abnormally high (tachygastria) or low (bradygastria) slow wave frequency.[7,8]

Our study shows that in children with symptoms of non-ulcer dyspepsia abnormal fasting and fed electrogastrography patterns could be discerned, whereas control children without any history of gastrointestinal disorder showed a normal electrogastrographic pattern, with only short periods of arrhythmia. Children with recurrent unexplained symptoms of upper intestinal dysfunction are commonly encountered in paediatric clinical practice and can represent a diagnostic challenge for paediatricians. Recent studies have shown that fasting and/or fed gastrointestinal motor abnormalities can be recorded by manometry in a high proportion of children presenting with symptoms of non-ulcer dyspepsia. These abnormalities included antral and/or duodenojejunal hypomotility, and uncoordinated antroduodenal motility[2–4,21] and furthermore, delayed gastric emptying has been detected in most of these patients.[3]

The fact that a large proportion of our patients with dyspepsia and delayed gastric emptying showed gastric arrhythmias is not unexpected as motor events of the stomach are controlled by electrical activity of gastric smooth muscle cells. Abnormal electrical activity of the stomach might disturb motor events either by destroying the orderly patterns of gastric peristalsis or by inhibiting strength of muscular contractions.[22] Whatever the mechanism involved, gastric propulsion and emptying are impaired, and dyspeptic symptoms such as nausea and vomiting can ensue. Recent data in adults indicate that electrogastrography can be used as a screening test in the diagnostic assessment of patients with symptoms suggesting gastric motility disorders.[23] Furthermore, the test seems to be of value in distinguishing functional from mechanical gastroparesis.[24]

The commonest arrhythmia described in patients with gastric electrical abnormalities is tachygastria; however, in our patients periods of bradygastria were encountered more frequently than tachygastria. If tracings were anlaysed on the basis of distribution of electrogastrography power, patients with non-ulcer dyspepsia were differentiated from controls for the low frequency range both in the fasting and fed state, and for high frequency ranges only during fasting period. Interestingly, four patients, whose electrogastrography showed a prevailing pattern of bradygastria in the fasting state, developed periods of increased frequency after feeding.

The neurohumoral mechanisms involved in the production of arrhythmias are unknown.[22] Gastric arrhythmias can be induced both in dogs and in humans by agents such as prostaglandin E_2, adrenaline, glucagon, and metenkephalin.[25–27] Local prostaglandins seem to mediate the occurrence of arrhythmias by adrenaline and metenkephalin, whereas glucagon seems to induce gastric arrhythmias by a nonprostaglandin mediated mechanism.[26] Whether gastric arrhythmias and dyspeptic symptoms arise from an abnormal release of some of the above mentioned agents in the circular muscle or at level of myenteric plexus of intestinal wall is still unknown. The correlation of gastric arrhythmic patterns with neuroendocrine measures and with dyspeptic symptoms would require more extensive evaluation.

Previous studies have indicated that gastric arrhythmias occur rarely after feeding, most likely because postprandial mechanical and neurohormonal changes might make the stomach less susceptible to arrhythmia.[28,29] On the other hand, there is experimental evidence that inhibition of cholinergic activity cases shortening of refractory periods of smooth muscle cells and increases slow wave frequency.[30] It is tempting to suggest that in patients with non-ulcer dyspepsia defective release of acetylcholine from intramural cholinergic nerves or the effects of arrhythmic agents might give rise to both occurrence of gastric electrical arrhythmias and decreased motility.

In our view, there is reason to believe that electrogastrography is a promising technique in the diagnostic approach to patients complaining of recurrent symptoms suggesting functional gastrointestinal disease and without organic explanation for their symptoms. Both electrogastrography and gastric emptying time measurement can be helpful in identifying altered gastric function. Such information may be quite useful in establishing a correct diagnosis and in directing a viable management plan. However, the question of how specific and sensitive the findings of gastric arrhythmias are in patients with unexplained gastrointestinal functional symptoms remains to be answered. In addition, it remains to be established whether drugs normalise the arrhythmias and relieve the patient's symptoms.

Presented in part at the Digestive Disease Week, New Orleans, Louisiana, USA, 19–22 May, 1991

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Archives of Disease in Childhood 1992; **67**: 618–621

Gaviscon and Carobel compared with cisapride in gastro-oesophageal reflux

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Accepted 18 January 1992

Abstract

We compared the efficacy of the prokinetic agent cisapride with that of Gaviscon (an alginate/alkaline compound) plus Carobel (carob seed flour) in the treatment of gastro-oesophageal reflux (GOR). Fifty infants with confirmed GOR received either oral cisapride (0·8 mg/kg/day) or Gaviscon plus Carobel for one month in a randomised, parallel group study. Parental evaluations, diary scores, and 24 hour lower oesophageal pH recordings before and at the end of each treatment were compared.

In the cisapride group 14/26 (53%) were considered better by their parents compared with 19/24 (79%) of those who received Gaviscon plus Carobel. Diary scores, range (0·00–1·00), improved in both groups with the median change being greater in the Gaviscon plus Carobel group (−0·21) than the cisapride group (−0·15). Five of 17 pH variables had significantly improved from baseline in infants who had received cisapride compared with 11/17 in those receiving Gaviscon plus Carobel. However, unpaired analysis of diary and pH data showed no significant differences between the two groups. We conclude that first line treatment of GOR with cisapride is no more effective than conventional treatment with Gaviscon plus Carobel.

Gastro-oesophageal reflux (GOR) is a common disorder of infancy. It is frequently mild and self limiting[1 2] but can cause serious morbidity and even mortality.[3] Conventional management consists of advice on posture, the use of antacids, and thickening of feeds.[4] Preliminary studies suggest that cisapride, a novel, gastrointestinal, prokinetic agent is a valuable drug in the treatment of GOR in infants and young children.[5 6] Gaviscon, an analginate/alkaline compound (Reckitt and Colman), has been shown to diminish reflux in a double blind, placebo controlled study.[7] These two forms of treatment act in very different ways. Cisapride stimulates cholinergic receptors in the enteric plexus,[8] and improves both oesophageal motility[9] and gastric emptying in adults,[10] whereas the mode of action of Gavison is less clear cut. It is believed to form a thick, foamy raft on the surface of gastric contents,[11] which coats the fundus of the stomach and protects the oesophagus from peptic ulceration. Direct buffering of gastric acid, resulting in a neutral refluxate is probably of subsidiary importance. Carobel, a thickening agent made from carob seed flour (Cow and Gate), is thought to render feeds more viscous, making regurgitation less likely. In the present study the relative effectiveness of Gaviscon plus Carobel and cisapride in infants with symptomatic GOR is assessed. We report our findings in a randomised, parallel group trial conducted over a one month period utilising both clinical criteria and lower oesophageal pH monitoring.

Patients and methods

PATIENTS

Fifty bottle fed infants with chronic vomiting, aged between 2 and 18 months, had GOR confirmed by 24 hour lower oesophageal pH monitoring (that is, a pH less than 4 for at least 5% of the recording period). None had evidence of significant neurological, respiratory, metabolic or associated gastrointestinal disease, or had received H_2 antagonists, theophylline, or anticholinergic drugs. Infants were randomly allocated either oral cisapride 0·2 mg/kg/dose four times a day (group A) or infant Gaviscon half a sachet to each 90 ml feed (group B) for four weeks. Carobel was also prescribed for those infants in group B who were not fully established on solid foods. The study was approved by the Leicester Health Authority ethics committee and informed consent was obtained from parents in all cases.

CLINICAL ASSESSMENT

Parents were provided with a diary in which a daily record of vomiting was kept. Severity was graded as follows: absent (0), 1–4 episodes per day (1), or greater than 4 episodes per day (2). The final score was calculated by dividing the sum of the daily scores by the maximum score possible for the number of days for which records were available, range 0–1·00. This facilitated a comparison of scores between groups A and B, by allowing for small differences between the groups in the number of days for which diaries were kept. A subjective parental evaluation of treatment was also obtained at the end of the study.

OESOPHAGEAL pH MONITORING

Lower oesophagel pH monitoring was performed using a 2·1 mm diameter flexible antimony electrode monocrysant model 91–0011 (Synectics Medical) which was passed nasally and advanced into the fasting stomach. The probe was then withdrawn to a distance equivalent to 87% of the total oesophageal length, calculated using the formula of Strobel *et al.*[12] The semidisposable electrodes were calibrated before and after each test at pH 1 and 7 at 23°C. Electrodes were discarded if deviations of 0·2 pH units or more from either standard buffer occurred. A reusable silver/silver chloride reference electrode model 4011 (Synectics Medical) was secured to the chest wall and both electrodes were attached to a portable pH recorder and data storage system (Digitrapper Mark II, Synectics) which sampled intraoesophageal pH every four seconds. A reflux episode was defined as a fall in pH to below 4 for 15 seconds or longer. The lightweight device was easily carried by parents in a shoulder bag. No restrictions were placed on activity or diet during the 24 hour study period. On completion of each study the stored data were transferred on to an Amstrad PC 1512. Using dedicated software 'EsopHogram' (Gastrosoft Inc) the following variables were computed: (i) number of reflux episodes, (ii) number of reflux episodes >5 minutes, (iii) the longest reflux episode, and (iv) the percentage of the time during which reflux occurred, also known as the 'reflux index'. These were calculated for postprandial periods (within two hours of a feed), fasting periods (two hours or more after feeding), overnight (10 pm–6 am), and the total recording time. The total number of episodes and the number of episodes >5 minutes were expressed as an average rate per hour to allow for individual variations in the number and duration of feeds. Acid clearance values for postprandial and fasting periods were also calculated and expressed as minutes per reflux episode.

STATISTICAL METHODS

Contingency tables were constructed and χ^2 tests with Yates's correction factor were employed to determine the significance of differences in parental assessment between the two treatments. As the ages of infants, diary scores, and pH variables were not normally distributed non-parametric tests were employed. Changes in pH variables after treatment were analysed using Wilcoxon signed rank tests and significance was defined as p<0·05. Median values were calculated for pH variables. Differences between the two groups were assessed using the Mann-Whitney U test.

Results

All 50 infants completed the study. Twenty six had received cisapride (group A) and 24 Gaviscon (group B). Twenty one of the latter group were also given Carobel (1–2 scoops to each 90 ml feed). Table 1 gives clinical details of the two groups which were comparable in age, weight, reflux indices, and symptom scores during the pretreatment phase. Both medications were well tolerated; in group A two infants developed mild diarrhoea which did not interfere with the study, and another, after completion of the trial, had oesophagitis diagnosed at endoscopy while receiving cisapride.

SUBJECTIVE PARENTAL EVALUATION

Fourteen of 26 infants (53%) on cisapride were considered to have improved compared with 19/24 (79%) of those on Gaviscon plus Carobel, p=0·055 (χ^2 test).

DIARY SCORES

Scores for the 'run in' period and only the last two weeks of treatment were analysed. In group A 22/26 diaries were sufficiently complete for analysis, 16/22 (72·7%) had improved scores, median change −0·15 with 95% confidence intervals −0·26 to −0·01, p<0·05. In group B 18/24 diaries were suitable for analysis. Fifteen out of 18 (83·8%) had improved, median change −0·21 with 95% confidence intervals −0·39 to −0·11, p<0·01. The difference between the changes that occurred on treatment in the groups was not statistically significant (Mann-Whitney U test).

OESOPHAGEAL pH MEASUREMENTS

Seventeen variables were analysed in each group (tables 2 and 3). In group A 5/17 showed significant improvement compared with 11/17 in group B. The reflux index and the number of episodes exceeding five minutes improved on both treatments. Direct comparison between the two groups of changes in each pH variable revealed no significant differences.

Discussion

The clinical importance of uncomplicated GOR is a matter for debate. In the absence of overt oesophagitis, failure to thrive, apnoeic spells, or

Table 1 Patient details at recruitment. Results are median (range)*

	Group A· cisapride (n=26)	*Group B Gaviscon (n=24)*
Age (months)	4·0 (2–18)	4 5 (2–17)
Weight (kg)	6·5 (3·0–15 0)	6 3 (3·9–8·9)
Total reflux index (%)	15 3 (5·3–71·0)	15·0 (5·1–36 5)
Vomiting score (0–1 00)	0 73 (0 29–1)	0 69 (0 23–1)
Male:female ratio	15.11	15 9

*There was no significant difference between groups A and B for any variable by Mann-Whitney U test.

Table 2 Oesophageal pH results in group A (cisapride, n=26). Results are median (range)

	Before treatment	*After treatment*	*Wilcoxon signed rank test*
Postprandial·			
No of episodes/hour	2 4 (0 6–15 0)	1·8 (0·1–10 1)	NS
No of episodes >5 min/hour	0·5 (0 0–10 0)	0·3 (0·0–1 3)	NS
LRE (min)	26·0 (4 0–120·0)	17·5 (1 0–120 0)	NS
Reflux index (%)	20·1 (4 9–62·0)	10·9 (1 8–60·0)	NS
Clearance (min/reflux)	3·1 (0 5–20 0)	2·6 (0 1–14·0)	p<0·01
Fasting·			
No of episodes/hour	1 6 (0 5–3 2)	1 4 (0 4–6 5)	NS
No of episodes >5 min/hour	0 5 (0 0–1 2)	0 2 (0 0–1·2)	p<0 05
LRE (min)	31·0 (2·0–301·0)	22 0 (1·0–244 0)	NS
Reflux index (%)	13 6 (0·7–92·0)	8·7 (0·3–90 0)	p<0 05
Clearance (min/reflux)	3 8 (0·6–15 5)	2·6 (0·9–7 1)	NS
Overnight:			
No of episodes/hour	1·1 (0·0–3·6)	0·6 (0 0–7 1)	NS
No of episodes >5 min/hour	0·4 (0 0–1 0)	0·1 (0 0–1 5)	NS
LRE (min)	28·0 (0 0–172·0)	6 5 (0 0–102	NS
Reflux index (%)	10·4 (0 0–60 7)	5 8 (0 0–85·4)	NS
Total:			
No of episodes/hour	2 0 (0 9–10·8)	1 7 (0 1–7·9)	NS
No of episodes >5 min/hour	0 5 (0 0–1·0)	0 2 (0 0–1·2)	p<0 05
Reflux index (%)	15·3 (5·3–57·5)	9 5 (0 3–82 8)	p<0 05

LRE=longest reflux episode

Table 3 Oesophageal pH results in group B (Gaviscon plus Carobel, n=24). Results are median (range)

	Before treatment	*After treatment*	*Wilcoxon signed rank test*
Postprandial:			
No of episodes/hour	2·1 (0·0–5·9)	1·3 (0·0–4·2)	NS
No of episodes >5 min/hour	0·3 (0·0–1·2)	0·1 (0·0–0·8)	p<0·01
LRE (min)	25·0 (0·0–99·0)	8·0 (1·0–120·0)	NS
Reflux index (%)	12·0 (5·0–48·8)	5·8 (0·0–33·3)	p<0·05
Clearance (min/reflux)	4·2 (0·0–17·2)	4·0 (0·0–31·0)	NS
Fasting:			
No of episodes/hour	1·5 (0·3–3·0)	1·2 (0·6–3·5)	NS
No of episodes >5 min/hour	0·4 (0·0–0·8)	0·2 (0·0–0·9)	p<0·01
LRE (min)	37·5 (4·0–140·0)	12·0 (0·0–300·0)	p<0·01
Reflux index (%)	16·5 (4·9–61·0)	7·1 (0·6–52·7)	p<0·01
Clearance (min/reflux)	6·9 (1·2–34·9)	3·5 (0·6–13·8)	p<0·05
Overnight:			
No of episodes/hour	0·9 (0·0–3·6)	0·4 (0·0–1·9)	NS
No of episodes >5 min/hour	0·3 (0·0–0·7)	0·1 (0·0–0·6)	p<0·05
LRE (min)	33·9 (0·0–128·0)	7·0 (0·0–252·0)	p<0·05
Reflux index (%)	10·1 (0·6–60·7)	4·0 (0·0–80·4)	p<0·05
Total:			
No of episodes/hour	1·8 (0·4–6·9)	1·4 (0·4–3·4)	NS
No of episodes >5 min/hour	0·4 (0·1–0·7)	0·1 (0·0–0·6)	p<0·01
Reflux index (%)	15·0 (5·1–36·5)	5·4 (1·9–42·3)	p<0·01

LRE=longest reflux episode.

recurrent pneumonia some clinicians recommend reassurance as the only treatment. Others believe that prompt treatment avoids complications. The distress to parents caused by frequent changes of clothing, alterations in feeding formulas, and the accompanying social incapacity are additional factors that influence the decision to prescribe specific treatment. In the present study of two recommended treatments, improvements were greater in the Gaviscon plus Carobel group than in the cisapride group as judged by clinical criteria and lower oesophageal pH measurements, but unpaired analysis failed to demonstrate a clear superiority of one treatment over the other. The general tendency towards improvement in both groups may have been real or fortuitous as the natural history of GOR over a one month study period is uncertain. The lack of a placebo control group precludes evaluation of either regimen in isolation.

A double blind design was not feasible for two reasons: first, to achieve the therapeutic effect at the desired time it was necessary to administer cisapride at least 30 minutes before a meal, whereas Gaviscon and Carobel had to be given during or after food. Second, there were differences in formulation that could not be overcome. Cisapride was only available as a liquid suspension and had to be given directly to the child, whereas Gaviscon and Carobel were in powder form and had to be mixed with the infant's formula at the time of feeding.

In pH terms, the best indicators of motility are the number of reflux episodes >5 minutes, the longest reflux episode, and the acid clearance time. The improvements seen in the number of reflux episodes >5 minutes and the longest reflux episode in the cisapride group during the fasting period are in agreement with other studies that demonstrate a prominent motility effect in the fasting period.[6] Cisapride's apparent lack of effect when the stomach is full is believed to be due to an increase in the frequency and duration of lower oesophageal sphincter (LOS) relaxations that result in more frequent reflux episodes.[13] The more rapid acid clearance values seen in the postprandial period of patients receiving cisapride suggest an early improvement in oesophageal motility. Phasic LOS relaxations are putatively responsible for the majority of reflux episodes, but low basal tone accounts for 20% of episodes[14] and becomes more important as oesophagitis progresses.[15] Motility studies in vomiting infants have shown that cisapride improves LOS tone[6] but concurrent pH studies in such infants failed to show a reduction in the number of reflux episodes, which reflects the degree of competence of the LOS. In the present study, no significant effect on the number of reflux episodes was observed in patients who received either treatment.

GOR occurs less frequently in the sleeping state than in wakefulness,[16] but the degree of overnight reflux may be predictive for the development of stricture and the need for antireflux surgery.[17] Gaviscon plus Carobel reduced these overnight measures of GOR severity considerably (table 3) whereas the changes achieved by cisapride were not significant.

One difficulty in interpreting the results of pH studies in infants with GOR is the buffering effect of milk on acid resulting in neutral reflux. Some investigators have overcome this problem by acidifying feeds during the test period. This is not feasible in any study with Gaviscon because acid added to feeds would have been neutralised by the alginate/alkali compound. The mechanism(s) whereby Gaviscon exerts a therapeutic effect is not fully known. It produces a viscous raft on the surface of gastric contents protecting the oesophagus from acid reflux. However, a recent study has shown that Gaviscon must be taken 30 minutes after food for raft formation to occur.[18] It did not occur when the drug was taken before or with a meal. Moreover, Laitinen *et al* have shown that sucralfate and Gaviscon taken 30 minutes before meals (when raft formation is unlikely) relieved symptoms and healed oesophagitis.[19] It is unlikely that the effects of Gaviscon are due to its buffering properties as Gaviscon is not primarily an anticid. Any such effect would have been least during fasting and overnight when feeding is infrequent. However, significant improvement was observed at these times after treatment; acid clearance times were also more rapid and in keeping with the improvements seen in vomiting scores. These findings suggest that Gaviscon improves motility indirectly, perhaps by alleviating oseophagitis, which is a recognised cause of impaired oeosphageal motor function.[15 20] Alternatively, Gaviscon in the lower oesophagus may have coated the pH electrode rendering the pH data uninterpretable. This is unlikely as electrode coating was not observed in an in vitro study of Gaviscon.[21]

As judged from pretreatment pH data, many infants had severe GOR and perhaps oesophagitis.[22] Routine endoscopy in infants presenting *de novo* with symptoms of GOR was not undertaken. None had received Gaviscon or cisapride before inclusion in the study and it seemed reasonable to proceed conservatively and treat with one or other regimen in the first instance. A poor response would have prompted investigation, and by this criterion only one infant was assessed endoscopically.

No attempt was made to assess the individual contribution of Carobel as our aim was to compare the new medication, cisapride, with conventional treatment, including Carobel.[4] A previous study has shown that Carobel alone improves reflux severity but that it is not as effective as cisapride in reducing vomiting due to GOR.[8] There were too few patients to allow comparison between the infants treated with Gaviscon plus Carobel and those with Gaviscon alone. Two previous studies, however, have shown that feed thickening may increase rather than decrease acid exposure in the lower oesophagus.[23–24]

Another potential difficulty relates to the degree of reproducibility of pH studies. Vandenplas *et al* found good correlation between results performed on consecutive days in the same group of patients,[25] whereas Hampton *et al* found a fourfold variation in results from tests done on consecutive days.[26] Simultaneous lower oesophageal pH monitoring with two probes shows good agreement,[27] which suggests that this variability is related more to biological than to technical factors. There is little doubt that lower oesophageal pH measurement is very useful diagnostically, but because of variations in the severity of GOR over relatively short periods of time, its value in following the progress of patients on medication may be more limited.

Significant reflux can sometimes occur in the absence of vomiting.[28] However, we chose to regard vomiting as one indicator of reflux severity because it was easy to observe and objective. Features such as irritability, 'chestiness', and poor feeding were rejected as too subjective and not specific for GOR. In the absence of a 'gold standard' method for monitoring the progress of GOR, it seemed reasonable to combine parental impressions, diary score assessments, and the findings from lower oesophageal pH studies to determine the response to treatment of the infants studied despite the recognised limitations of each assessment method.

In conclusion, cisapride is no more, and perhaps less effective than conventional treatment with Gaviscon plus Carobel. Thus, in GOR in infancy, the current practice of prescribing Gaviscon plus Carobel as first line treatment appears justified. However, our findings raise further questions. Should endoscopic assessment be a primary investigation in infants presenting with severe GOR as the presence of oesophagitis might indicate the need for an H_2 antagonist in addition to standard treatments. Further studies are also needed to clarify the relative efficacy of Gaviscon and Carobel.

We wish to thank Janssen Pharmaceuticals for providing generous financial support, the paediatricians at Leicester Royal Infirmary for referring patients and, not least, the parents who volunteered their children for this study

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Archives of Disease in Childhood 1992; **67**: 622–624

Should audio recordings of outpatient consultations be presented to patients?

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Accepted 31 December 1991

Abstract

Three hundred and four new and return paediatric outpatient consultations were tape recorded. Questionnaires (and tapes) relating to the experience were returned from 286 families. They showed that tapes had been helpful to more than 99% of parents and grandparents. The main benefits were in refreshing the memories of those who attended the consultation and in helping the understanding of those unable to attend. More than 70% of tapes were listened to more than once and a third of families made a copy. Most parents considered that all consultations should be taped.

The outpatient consultation provides the major source of information for patients who require specialist assessment. However, patients feel that information given by doctors is unsatisfactory[1,2] and this may relate in part to doctors' poor communication skills.[3,4] Even if doctors improve their performance in communication, patient understanding and recall of information will probably remain at a low level due to time constraints, the formal atmosphere of some clinics, and the fallibility of human memory. In paediatrics, the problem is compounded by the understandable inability of some parents to give their full attention while looking after the needs of their children.

Despite the improved conditions in many outpatient departments the consultation remains a single event, but the learning and understanding process in most cases requires repeated exposure to the same information. Butt in 1977 considered this problem and suggested providing an audiotape of the consultation.[5] This approach has been used in two studies of consultations involving patients with cancer.[6,7] In both studies, patients and doctors found it valuable, although recall of factual information was no greater than for conventional consultations without tape recording.

Table 1 Questionnaire (A): before consultation. Results are number (%) responding

Question	*Response*
(1) Do you agree to the consultation being taped? (n=376)	
Yes	365 (97·1)
No	11 (2·9)
(2) Do you wish to listen to the tape at home? (n=365)	
Yes	304 (83·3)
No	61 (16·7)
'Yes' to question 2:	
(3) Who do you think may find it useful? (n=304)	
Myself/ourselves	84 (27·6)
Others not attending	76 (25·0)
Both of these	144 (47·4)
(4) Who do you think would wish to listen to it other than yourself? (n=304)	
Partner	205 (67·4)
Grandparents	291 (72·0)
Other relative	56 (18·4)
Siblings	29 (9·5)
Friends	33 (10·9)
Doctor	11 (3·6)
Head teacher	3 (1·0)
'No' to question 2:	
(5) Why do you not wish to listen to the tape? (n=61)	
No play back facility	4 (6·7)
Other responses, for example, "not necessary', 'we know about the problem', 'we're both here'	57 (18·8)

It is important that patients and families are satisfied with an outpatient consultation and have the fullest possible understanding of their problem regardless of its nature and seriousness. Indeed some of the greatest anxieties for families, and the most difficult and time consuming consultations for doctors, are for conditions for which there are no serious implications and which are commonly variations of normal behaviour and health.

This study aimed to determine whether families presenting to general and specialist paediatric outpatient clinics find tape recording of consultations useful and perceive a need for such a service.

Methods

Four hundred consecutive adults with a child attending general paediatric and lipid and metabolic specialist paediatric outpatient clinics at the Children's Hospital, Birmingham during the period January to April 1991, took part in the study. They were given an explanatory leaflet about the tape recording and were asked to complete a questionnaire (A) on reporting to the clinic and before seeing a doctor (the author). Only one of two or more adults in attendance according to their choice was asked to complete the form. The questions are shown in table 1.

The questionnaire in English was passed from parent/guardian to the doctor at the start of each consultation. If it stated agreement to tape record the consultation and indicated a wish to take the tape home, the consultation was recorded.

A portable battery/mains operated Sony TC-D3 stereo cassettecorder with plug in microphone (dimensions 12 cm×8 cm×3 cm) was used to record on to C90 audiotape cassettes. The microphone and recorder were placed on a desk within two metres of each sitting position of doctor and parent(s)/guardian(s) at the start of each consultation.

On completion of the consultation, parent(s)/guardian(s) were given the tape and another questionnaire (B). They were asked to complete the questionnaire after listening to the tape and to return the tape and questionnaire by post or at a future consultation if planned.

Results

The questionnaire given before consultation (A) was completed by 376 parents/guardians (94·0%) (table 1). The majority were mothers (84·0%). Twenty four could not complete it due to language difficulties despite interpretation assistance. (Punjabi was the commonest first language after English of those completing the questionnaire.) Of 376 positive responders, 304 (83·9%) wished to listen to the tape at home. Two hundred and twenty (72·4%) thought that people other than themselves would wish to listen to it. Grandparents were cited most often (219; 72·0%).

The questionnaire given after consultation (B) with tape was returned completed by 289 parents (95·1%) (table 2). First or new patient consultations accounted for 31·8% of tapes. All but three of the tapes were listened to by parents. There was one recording failure. Grandparents listened to more than half the tapes (52·8%). Nearly all of the tapes were reported to be helpful when listened to by parents (99·6%), grandparents (99·3%), and other relatives (97·9%). More than two thirds of these felt the tapes were very helpful; refreshment of memory was the commonest stated reason for this (94·7%).

Seventy percent of tapes were listened to more than once and a third of families made their own copies (33·6%). The great majority of responders felt that all consultations should be taped (91·3%) and almost all felt that tape recorded consultations should be complemented by the sending of copies of consultant letters to family doctors. Seventy seven percent of questionnaires contained positive statements about the service in the 'any other comment' section.

The mean tape length for new patient consultations was 34 minutes 25 seconds (range 10 minutes 52 seconds–72 minutes 22 seconds) and for patients on repeat visits 14 minutes 26 seconds (range 5 minutes 10 seconds–54 minutes 36 seconds). Tape handling and the setting up of the recording took approximately 30 seconds for each consultation.

Table 2 Questionnaire (B): after consultation and listening to tape Results are number (%) responding

Question	*Response*		
(1) Is this a first consultation with the doctor or a return visit? (n=289)			
First	92 (31·8)		
Return	197 (68·2)		
(2) Could you hear the tape clearly? (n=289)			
Yes	286 (99·0)		
No	1 (0·3)		
	(2 tapes not listened to)		
(3) Who listened to the tape? (n=286)			
Parents	285 (99·7)		
Grandparents	151 (52·8)		
Other relatives	49 (17·1)		
Siblings	45 (15·7)		
Friends	40 (13·9)		
(4) Was it helpful? (n=286)	*Yes*	*Not reported/no*	
Parents (n=285)	284 (99·6)	1	
Grandparents (n=151)	150 (99·3)	1 (0·7)	
Other relatives (n=49)	48 (97·9)	1	
Siblings (n=45)	16 (35·6)	29 (64·4)	
Friends (n=40)	—	40 (100)	
How helpful?	*Very*	*Fairly*	*Slightly*
Parents (n=285)	255 (89·5)	30 (10·5)	0
Grandparents (n=151)	136 (90·7)	0	0
Other relatives (n=49)	35 (72·9)	13 (27·1)	0
Siblings (n=45)	16 (35·6)	0	0
Friends (n=40)	—	—	—
(5) If you found it helpful, why was that? (parent(s) only (n=285)			
Refreshed my/our memory	270 (94·7)		
Gave information I/we hadn't taken in	166 (58·2)		
Made me/us less worried	47 (16·5)		
Helped understanding of interested people who could not attend consultation (n=153)	149 (97·4)		
(6) Did anyone listen more than once? (parent(s) only n=285)			
Mothers	41 (14·4)		
Fathers	29 (10·2)		
Both	132 (46·3)		
(7) Did you copy the tape? (n=289)			
Yes	97 (33·6)		
No	192 (66·4)		
(8) Would you agree to students listening to the tape? (n=286)			
Yes	284 (99·3)		
No	2 (0·7)		
(9) If taping of consultations were routine, would you still wish to receive a copy of the consultant's letter to your family doctor (n=289)			
Yes	287 (99·3)		
No	2 (0·7)		
(10) Should consultation tape recording be used for all, some, or none of the consultations? (n=287)			
All	262 (91·3)		
Some	25 (8·7)		
None	0		
(11) Any other comments (n=289)	Completed (positively) by 222 (76·8)		

Discussion

Tape recording consultations in busy outpatient clinics is practicable and relatively inexpensive. Tape handling time is short. Nearly all families have access to a cassette player. Technical failure should be negligible if professional standard equipment (costing less than £200 in this study) is used and mains operated. Failure was very low in this study using the battery operated option. Controlled seating arrangement is unnecessary; significant parts of the conversations in this study took place away from the starting sitting positions of the adults and by as much as 4 metres from the microphone. The 'write off' cost of cassettes not returned, which in this study amounted to fewer than 2% (nine of 15 were subsequently returned) can be offset by asking families to bring a cassette with them if they wish the consultation to be taped. Stock tapes can be available for those forgetting to bring them.

As this study involved a free extension to the more usual outpatient service, it is perhaps not surprising that there was a relatively high 'take up' rate to the offer to tape record consultations and make them available to families. However, the relatively high percentage response in returning questionnaires and tapes without funding or postal provision would seem to be strongly supportive of the positive reaction expressed in the questionnaire responses.

Perceived helpfulness of tape consultations by parents, relatives, and friends soon after listening to the tapes is clear from the results. Whether a similar response would be obtained at a later time has not been tested. Furthermore, accuracy of recall of information by families, or a change in their action as a result of the tape recording being available has not been assessed. However, if a successful outcome to a consultation can be measured in part by a positive reaction by parents, this approach is extremely useful. Unsolicited expressions of support, encouragement, and thanks in more than 75% of questionnaires cannot be ignored.

The reasons given by parents for tape recording being helpful suggest that all consultations and not just those involving children might benefit. There are particular problems for single attending parents taking in information and asking all the questions they would want to when their attention is repeatedly directed towards looking after the young child and away from the discussion. In many adult clinics, partners and friends, who might support the patient and have an interest in consultation, and who feel it may be inappropriate for them to attend, may also gain from taped consultations.

As with the practice of sending copies of consultant letters for family doctors to parents/patients, tape recording of consultations generates telephone calls for further information and clarification. This may be because parents/patients are positively encouraged in both cases to telephone myself as consultant. The 289 taped consultations led to 22 calls, which is similar to the number relating to copy letters (6·8%, personal observation). This study demonstrates that almost all parents consider the copy letter approach retains its importance even when consultations are recorded.

Previous smaller studies of taped consultations have demonstrated the usefulness of this approach for 'difficult and emotive' subjects. Almost all parents/patients have considerable anxieties when attending cosultations and many of the more difficult and time consuming problems relate to very limited or self resolving pathology or variations on normal health and behaviour. The case for tape recording can be made for all consultations, including repeat visits, and may be more appropriate than adopting a selective approach. This is certainly the view of the great majority of parents who have direct experience of this service.

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Archives of Disease in Childhood 1992; **67**: 625–627

Chloroquine in idiopathic pulmonary haemosiderosis

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Abstract

Two cases of idiopathic pulmonary haemosiderosis are reported in order to highlight the diagnostic problems, associated features, and the response to chloroquine, which is a new treatment for this life threatening condition.

Iron deficiency anaemia is common in childhood and usually dietary in origin.[1] If a deficient intake is not the cause, diagnostic attention normally focuses on the gastrointestinal tract. Respiratory causes are rare and occult pulmonary haemorrhage is often not considered until other possibilities have been exhausted.[2] We describe two children with primary pulmonary haemosiderosis in order to highlight some of the problems in making this diagnosis. We describe the response to chloroquine in order to draw attention to a novel treatment for this condition.

Case reports

CASE 1

When 4 years of age this previously well girl developed an erythema multiforme like rash which responded rapidly to oral steroids. Three months later the rash recurred, associated with cough, lethargy, and evidence of consolidation on the chest radiograph. The symptoms gradually remitted on steroids, but a high erythrocyte sedimentation rate (ESR) persisted. A year later she developed cough, weight loss, and dyspnoea. She was pale, a non-specific maculopapular rash was noted on the wrists and arms, and crackles were heard over both lung fields. Haemoglobin concentration was 62 g/l, with a hypochromic, microcytic picture, and the ESR was 82 mm/hour. The chest radiograph showed patchy shadowing in both lung fields. The serum iron concentration was 3·5 mmol/l (normal 11·5–27·0) and total iron binding capacity 39 mmol/l (normal 36–77). A bone marrow biopsy specimen showed no stainable iron and no evidence of malignancy, and a jejunal biopsy was normal. The initial diagnosis of atypical pneumonia was changed to cryptogenic fibrosing alveolitis, and she was given oxygen, blood transfusion, and steroids. She made a good clinical response. She remained well until she developed localised scleroderma (morphoea) confirmed by biopsy at 7 years of age. She always complied poorly with treatment, and her steroids were finally stopped at age 11 years.

Three years later she developed a cough and wheeze. An initial diagnosis of asthma was made, but a flow volume loop was restrictive in type, and she was referred to the Royal Brompton Hospital. On admission, she was tachypnoeic, but there was no digital clubbing. There was widespread morphoea, sparing the face. She had fine end inspiratory basal crackles. The chest radiograph showed predominantly basal reticulonodular shadowing with prominent hilar lymphadenopathy (fig 1). Other investigations were haemoglobin concentration 96 g/l, with a hypochromic, microcytic picture; white cell count $12{\cdot}0\times10^9$/l, platelets 581×10^9/l, and ESR 126 mm/hour. Serum iron concentration was 7·5 mmol/l, iron binding capacity 46 mmol/l, ferritin 202 μg/l (normal 15–300), and urea and electrolytes were normal. Lung function (percent predicted) results were: forced expiratory volume in one second (FEV_1) 31, forced vital capacity (FVC) 29, total lung capacity (TLC) 66, residual volume 215, and whole lung carbon monoxide transfer (TLCO) 27. At fibreoptic bronchoscopy the lower respiratory tract was macroscopically normal. The transbronchial biopsy specimen showed large numbers of haemosiderin laden macrophages within alveoli (fig 2). There was also haemosiderin impregnation of elastin in the alveolar wall and the walls of blood vessels. No other pathological features were seen in the specimen. These findings confirmed the clinical diagnosis of idiopathic pulmonary haemosiderosis. The bronchoalveolar lavage was technically unsatisfactory. She was started on chloroquine sulphate 200 mg daily. Her ESR fell to 15 mm/hour, she required no further transfusions, her chest symptoms disappeared, and her chest radiograph cleared (fig 3). At age 16 she developed pyoderma gangrenosum.

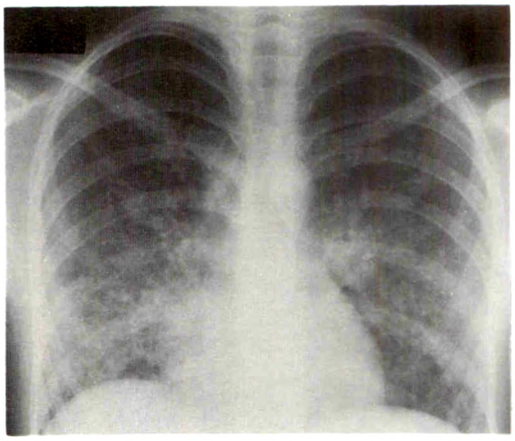

Figure 1 Chest radiograph of case 1 on admission to the Royal Brompton Hospital. There is prominent hilar lymphadenopathy with predominantly basal reticulonodular shadowing.

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Accepted 8 January 1992

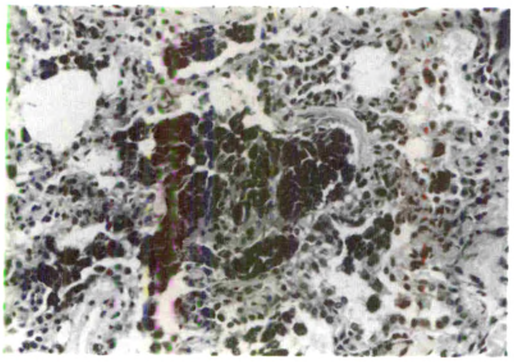

Figure 2 Transbronchial lung biopsy specimen of case 1. Haematoxylin and eosin preparation showing dark haemosiderin within the cytoplasm of macrophages within alveoli (magnification ×400).

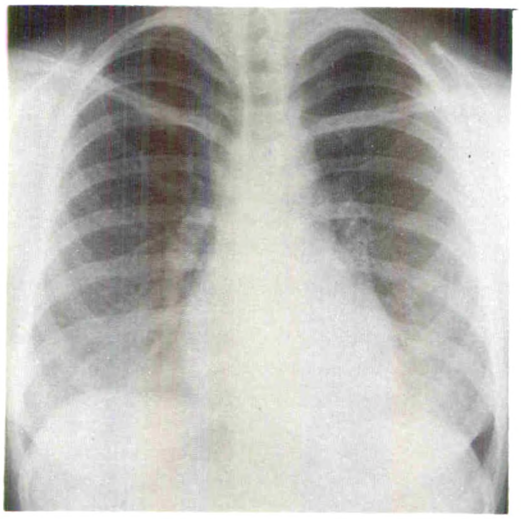

Figure 3 Chest radiograph of case 1 one year after starting chloroquine. There has been substantial clearing of the shadowing and regression of the lymphadenopathy.

Barium enema was normal. Now aged 17 years, she continues on chloroquine, and has had only mild relapses of pulmonary haemorrhage, which responded promptly to steroids. When last seen, her lung function had improved (FEV_1 71%; FVC 86%; TLC 92%; TLCO 49%) and her chest radiograph was nearly normal.

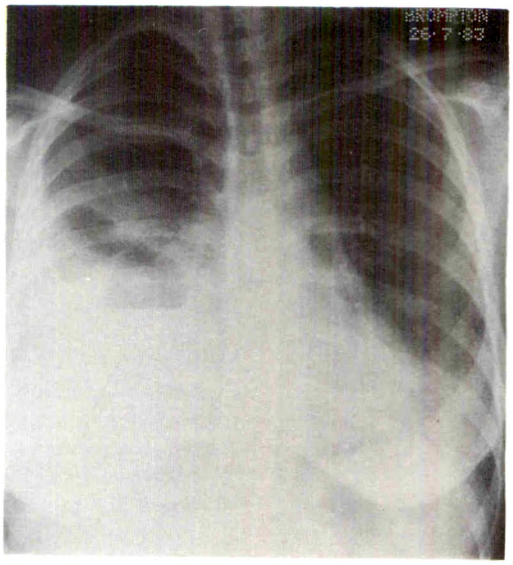

Figure 4 Chest radiograph of case 2 after her open lung biopsy. There are air-fluid levels in the right hemithorax completely obscuring the lung field. On the left there is basal reticulonodular shadowing. At right thoractomy a loculated pleural effusion was found.

CASE 2

At 13 years of age this girl was found to have a profound iron deficient anaemia despite adequate intake and no evidence of excessive blood loss or malabsorption. Two years previously, at the time of an appendicectomy, her haemoglobin concentration had been normal. She was noted to have a cough and haemoptysis, with a chest radiograph reported as showing evidence of consolidation. Despite being transfused, her anaemia recurred, and further negative investigations included faecal occult bloods, barium meal and follow through, oesophagoscopy, bronchoscopy (bronchoalveolar lavage and transbronchial biopsy not performed), colonoscopy, jejunal biopsy, and rectal biopsy. Urinary haemosiderin and sediment and renal function were all normal. Ten months after her initial presentation the chest radiograph revealed granular shadowing, and the diagnosis of idiopathic pulmonary haemosiderosis was established by open lung biopsy. The procedure was complicated by a pneumothorax, and subsequently an encysted pleural effusion developed (fig 4). After decortication she was treated with prednisolone 60 mg and azathioprine 100 mg daily. She was also given high dose steroids by Nebuhaler, an empirical trial of a gluten free diet, and intensive plasmapheresis, but she continued to have haemoptyses and remained transfusion dependent (two units of packed cells every one to two months). Four years after her initial presentation she was started on chloroquine sulphate 200 mg twice daily. Her other treatment was slowly withdrawn and she remained transfusion independent with only occasional very slight haemoptyses, one in association with influenza immunisation. Three years later chloroquine was discontinued, but within six months she had relapsed. Chloroquine 200 mg daily was restarted and the disease remitted. However, retinal changes were detected during a routine ophthalmological check. These were reversed when chloroquine was discontinued. Unfortunately she has had further relapses and we were advised that she could not safely be treated with chloroquine again. Her renal function and antiglomerular basement membrane antibodies have remained normal. Currently she is receiving corticosteroids and cyclophosphamide to try to control her disease.

Discussion

These children are highly selected referrals to a tertiary centre and illustrate the difficulty of establishing the diagnosis of a rare cause of a common problem. Both children presented with iron deficiency anaemia, with only case 1 having a history of a previous respiratory illness, which in retrospect may have been due to pulmonary haemosiderosis. The delay between first onset of symptoms and diagnosis was 10 years in this child, and several months in the second case. During this time many unpleasant, invasive, and non-contributory investigations were performed, which might have been avoided if the diagnosis had been considered earlier.

Idiopathic pulmonary haemosiderosis can present at any age from the neonatal period to late adulthood.[3–5] The usual presentation is with iron deficiency anaemia, which may initially respond to oral iron.[3] The classical triad of unexplained anaemia, haemoptysis, and pulmonary infiltrates is rare in childhood, only partly because bloodstained sputum is usually swallowed.[2] Half have no pulmonary symptoms.[5] Swallowed blood may lead to positive faecal occult bloods, mimicking gastrointestinal bleeding.[2] Rarer presentations are the febrile child with a bronchopneumonia like illness[5] and acute fulminating pulmonary haemorrhage.[2, 4] The physical signs may include digital clubbing and hepatosplenomegaly,[2, 3] with usually a clear chest to auscultation.[6] However, other than pallor, the child may appear completely normal on examination. Investigations may show eosinophilia,[3] and the chest radiograph may be normal, or show non-specific infiltrates, miliary shadowing, or confluent shadows.[3] Hilar and mediastinal lymphadenopathy may be present.[7] There is no correlation between pulmonary symptoms and radiographic abnormalities.[7] Lung function tests show restrictive physiology and reduced carbon monoxide transfer at rest and on exercise in the chronic phase.[3] In the acute phase carbon monoxide transfer rises by more than 30% above baseline and is associated with a fall in haemoglobin by 20–40 g/l and deteriorating radiographic changes over a 24 to 48 hour period.[8] Although the diagnosis can be made by finding haemosiderin laden macrophages in sputum or gastric washings,[5] a more direct approach is fibreoptic bronchoscopy with bronchoalveolar lavage and transbronchial biopsy.[9] Diagnosis can be established by open lung biopsy, but transbronchial biopsies should be interpreted cautiously, as haemosiderin laden macrophages within alveoli can be seen in other conditions including heart failure, pneumonia, primary pulmonary hypertension, and pulmonary veno-occlusive disease.[10] The clinical history is thus of vital importance to the pathologist. Unusual features in our cases include the association with erythema multiforme, morphoea, and pyoderma gangrenosum (case 1) and relapse in association with immunisation (case 2), neither of which has to our knowledge been described before.

The variable course and rarity of the disease makes assessment of treatment difficult; for example, a third child referred to us in the same period went into spontaneous remission (details not given). We elected to use chloroquine because of its lack of toxicity compared with immunosuppressive regimens that have been used[11] and because of isolated reports of a dramatic response in childhood cryptogenic fibrosing alveolitis.[12] Unfortunately, as in case 2, the use of chloroquine may be limited by retinal toxicity and regular ophthalmic checks are essential.

In a condition that shows spontaneous fluctuations in severity, it is difficult to be certain of the therapeutic benefit of any intervention. In case 2, a prompt decrease in the severity of her illness on starting chloroquine, together with a history of relapse on each of two occasions when chloroquine was stopped, strongly supports a real beneficial effect. Case 1 is more difficult to assess, in part because of poor compliance with medication, but it would seem probable that her improvement was related to chloroquine treatment.

In summary, we describe two cases of childhood idiopathic pulmonary haemosiderosis, one of whom also had several unusual skin rashes. We highlight the diagnostic difficulties and delays and describe our experience with chloroquine as a treatment for this disease. We suggest that a therapeutic trial of chloroquine should be considered in children with idiopathic pulmonary haemosiderosis.

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Archives of Disease in Childhood 1992; 67: 628–631

Abnormal serum IgG subclass pattern in children with Down's syndrome

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Accepted 1[illegible] December 199[illegible]

Abstract

Susceptibility to infections is a well known feature of Down's syndrome. The possible relation between this predisposition and the serum concentrations of the IgG subclasses was studied in 38 children with Down's syndrome aged 1–12 years. An age matched group of 50 healthy children served as controls. The serum concentrations of IgG_1 and IgG_3 were significantly raised among children with Down's syndrome in all three age groups studied (that is 1–2·5, 4–8, and 9–12 years). The serum concentrations of IgG_2 were normal in the first two groups but significantly reduced in the third age group. In contrast, the concentrations of IgG_4 among children with Down's syndrome were significantly reduced in all three age groups. Moreover, among the children with Down's syndrome aged 4–12 years 68% (15/22) had IgG_4 concentrations below 2 SDs of the geometrical mean of the controls The results may partially explain the proneness of children with Down's syndrome to infections with encapsulated bacteria. Although the underlying cause of these abnormalities is unknown, IgG subclass determination seems relevant in the clinical evaluation of children with Down's syndrome.

Susceptibility to infections is a feature of Down's syndrome, and is likely to be due to abnormalities of host defence, that is, of the immune response. Reported defects include components of cell mediated[1] and humoral immunity,[2] the inflammatory response,[3 4] and interferon production.[5 6] The results of studies of serum immunoglobulin concentrations in subjects with Down's syndrome have been conflicting. Both normal and raised serum concentrations of IgG, IgA, and IgE have been found and raised, normal, and decreased concentrations of IgD.[1 7] In adults with Down's syndrome the serum concentrations of IgG_2 and IgG_4 have been found to be significantly reduced and those of IgG_1 and IgG_3 to be normal or raised.[8] Recently it has been claimed that about half of the children with Down's syndrome are deficient in IgG_4.[9] The aim of the present study was to investigate the serum concentrations of all IgG subclasses in children with Down's syndrome and to compare them with those in healthy children of the same ages.

Patients and methods

The study comprised 38 non-institutionalised children with chromosomally verified Down's syndrome, 16 girls and 22 boys, who were aged 1 to 12 years. Nine of these patients had congenital cardiovascular malformations, none of which was of major clinical significance. Three of the patients had been operated upon in the neonatal period for treatment of congenital gastrointestinal malformations, and none of them suffered subsequently from any complications of these conditions. In the 38 children with Down's syndrome blood samples were taken for serum IgG subclass determination. A brief interview with the parents concerning the dietary habits of the children confirmed that they had a normal diet. The proneness to infectious diseases was evaluated and the children underwent physical investigation at the time of blood sampling. None of them showed signs of current infection at that time.

Fifty age matched healthy children served as controls and because of the age dependency of IgG subclass concentrations, particularly IgG_2 and IgG_4 in early childhood,[10] the children were split into three age groups: 1–2·5, 4–8, and 9–12 years. There were 16, 12, and 10 children with Down's syndrome and 20, 15, and 15 control children in the three age groups respectively.

The serum samples were stored at −20°C before analysis. The concentrations of the subclasses of IgG were determined by a competitive two step microtitre enzyme linked immunosorbent assay (ELISA) based on subclass specific monoclonal antibodies. The assay conditions regarding the buffers used, incubation times, and sample dilutions, and the specificity, sensitivity, linearity, precision, and accuracy will be described in detail elsewhere (C G M Magnusson, to be published). All serum samples were assayed in duplicate and a commercial standard serum (H00–03, Janssen, Belgium), calibrated against the WHO 67/97 standard,[11] was used to produce standard curves. The interassay imprecision, which was evaluated by including two dilutions of a control serum on each plate, gave coefficients of variation on seven different plates not exceeding 9% for all four subclasses.

The Mann-Whitney U test with correction for ties was used in the statistical analyses of the results and a two tailed $p<0·05$ was considered significant.

Results

The individual values and the geometrical mean concentrations and ±1 SD of the four IgG subclasses in the controls and children with Down's syndrome are presented in figs 1 and 2 and the table. There were no significant age

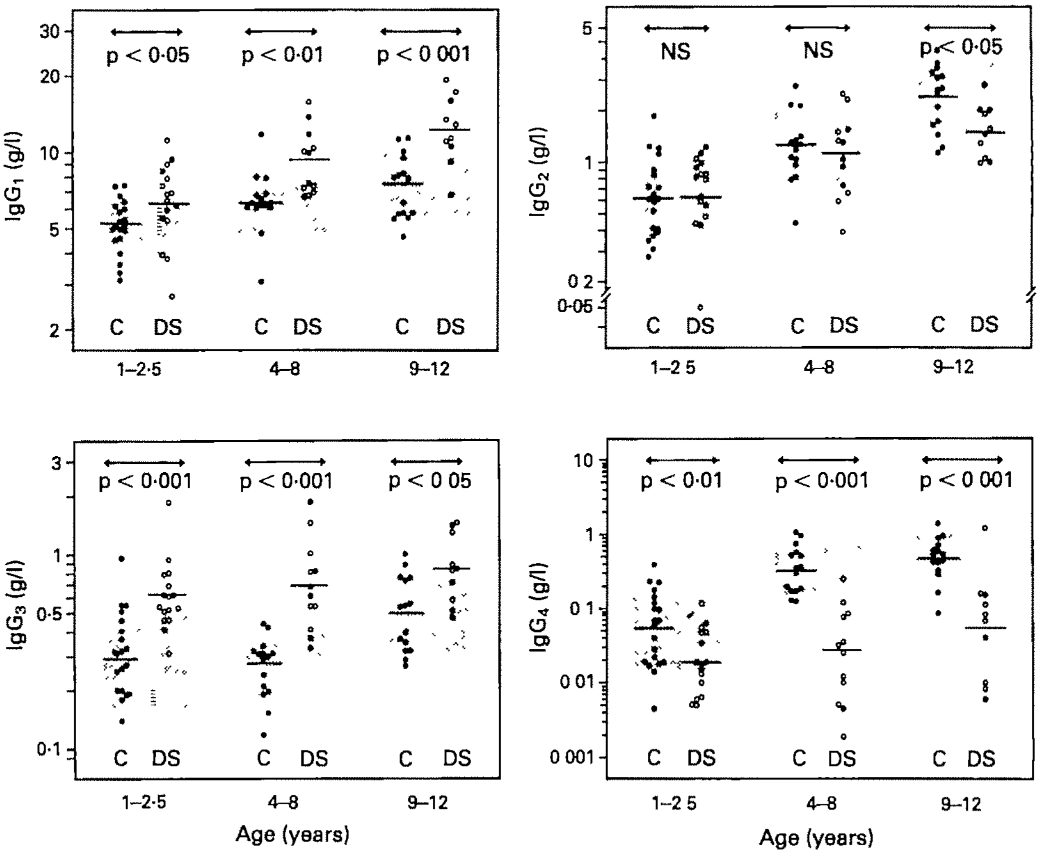

Figure 1 Individual and geometrical mean concentrations of the four IgG subclasses in children with Down's syndrome (DS) and control children (C). The children are split into three age groups (1–2·5, 4–8, and 9–12 years). The ±1 of the geometrical mean concentrations of healthy children are indicated (shaded area). The levels of significance are given in the figure

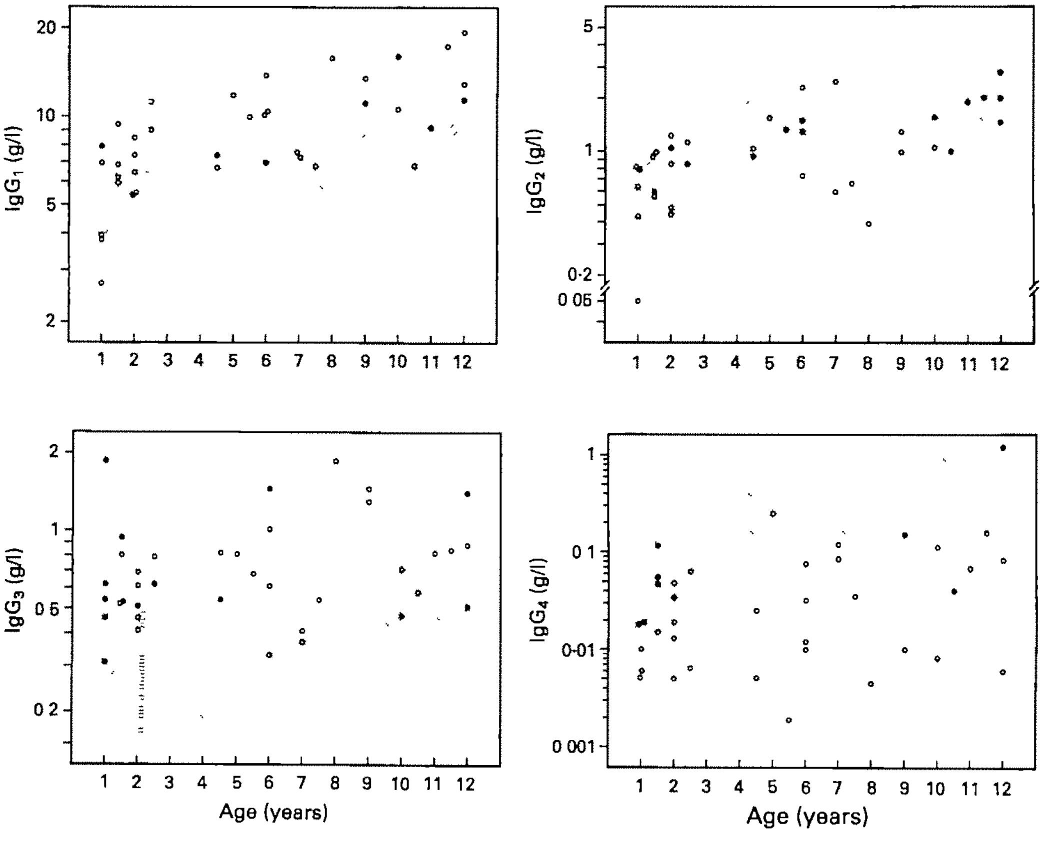

Figure 2 Individual concentrations of the four IgG subclasses in children with Down's syndrome in relation to age. The geometrical mean ±1 SD of healthy children are indicated (shaded area)

IgG subclass concentrations (g/l) in serum of children with Down's syndrome compared with healthy age matched control children in three age groups. Geometrical means (GM) ± 1 SD are presented

	Age groups (years)					
	1–2·5		*4–8*		*9–12*	
	Controls (n=20)	*Down's syndrome (n=16)*	*Controls (n=15)*	*Down's syndrome (n=12)*	*Controls (n=15)*	*Down's syndrome (n=10)*
Age (GM)	1·5	1·6	6·0	6·1	10·0*	10·7*
IgG$_1$ (GM)						
+1SD	5·1*	6·3*	6·4**	9·1**	7·3***	12***
−1SD	6·5	9·1	8·5	12	9·8	17
	4·0	4·5	4·8	6·8	5·5	9·0
IgG$_2$ (GM)						
+1SD	0·62	0·63	1·2	1·1	2·4*	1·5*
−1SD	1·0	1·3	1·9	1·9	3·6	2·2
	0·37	0·30	0·78	0·62	1·5	1·1
IgG$_3$ (GM)						
+1SD	0·29***	0·61***	0·26***	0·69***	0·49*	0·83*
−1SD	0·49	0·91	0·38	1·2	0·76	1·3
	0·17	0·41	0·18	0·41	0·32	0·55
IgG$_4$ (GM)						
+1SD	0·053**	0·019**	0·34***	0·024***	0·46***	0·057***
−1SD	0·17	0·52	0·69	0·10	0·92	0·29
	0·016	0·0072	0·16	0·0053	0·23	0·011

Calculated significance levels in Mann-Whitney U test. $^{*}p<0·05$, $^{**}p<0·01$, $^{***}p<0·01$

differences between controls and children with Down's syndrome in the two youngest groups, but the children with Down's syndrome were slightly older than the controls in the oldest age group (p=0·04) (table). The children with Down's syndrome had significantly higher concentrations of IgG$_1$ (figs 1 and 2, upper left) and IgG$_3$ (figs 1 and 2, lower left) than the controls in all three age groups. In contrast, the serum concentrations of IgG$_2$ were normal in the children with Down's syndrome in the two youngest age groups but significantly reduced among the oldest children with Down's syndrome (figs 1 and 2, upper right). The IgG$_4$ concentrations were significantly reduced in all three age groups of children with Down's syndrome (figs 1 and 2, lower right). In fact, in the two age groups with the oldest children, 68% (15/22) had IgG$_4$ concentrations below 2SD from the geometrical mean.

Discussion

The higher serum concentrations of IgG subclasses 1 and 3 in the children with Down's syndrome compared with the controls may well be a consequence of polyclonal stimulation from repeated bacterial infections, which obviously does not include IgG$_2$ and IgG$_4$. This contrast strengthens the concept that children with Down's syndrome fail to respond properly with antibodies of the latter subclasses. The results are in accordance with recent data for adults with Down's syndrome[8] and for children concerning IgG$_4$[9] and are likely to be of pathogenetic significance for the susceptibility to infections. It is interesting to note that IgG$_4$ deficiency is found in Down's syndrome at all ages,[8 9] but an IgG$_2$ deficiency tends to develop later in life among children and adults with Down's syndrome.[3] Thus the IgG$_4$ deficiency is not accompanied by an IgG$_2$ deficiency in childhood in Down's syndrome.

Children with Down's syndrome are especially prone to respiratory bacterial infections.[4] This may be partially explained by a deficiency in IgG$_2$ and IgG$_4$ antibodies, of which the former are known to be directed primarily against bacterial polysaccharide antigens of encapsulated bacteria, such as *Diplococcus pneumoniae* and *Haemophilus influenzae*.[12] Even though the serum concentration of IgG$_4$ is low, it may play a part in mucosal defence because of its higher relative concentration in secretions.[13] Virus specific IgG antibodies are often of subclasses 1 and 3.[12]

The mechanism underlying the abnormal serum IgG subclass pattern is probably not a gene dosage effect as none of the chromosome 21 genes are known to regulate immunoglobulin production. Secondary effects of either a factor related to immunoglobulin production or a deficiency of a trace element such as selenium[14] are proposed as alternative explanations. We have recently reported that selenium supplementation in children with Down's syndrome has a significant augmentative effect on the serum concentrations of IgG$_2$ and IgG$_4$, but not on those of IgG$_1$ and IgG$_3$.[14]

Although the mechanism behind the abnormal subclass pattern in individuals with Down's syndrome is unknown, it seems relevant to assay the IgG subclass concentrations among patients with Down's syndrome who have repeated infections. If only the total serum IgG concentration is assayed a deficiency in the IgG$_2$ and IgG$_4$ subclasses will escape detection.

The skilful technical assistance of Mrs Maggy Magnusson is acknowledged. This study was supported by grants from the Savstaholm Society, the Marcus Borgstrom Foundation, and the Swedish Medical Research Council (grants 5445 and 16X-105).

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The uses of laparoscopy[†]

If the October 1991 issue of the *Journal of Pediatric Surgery* is anything to go by, laparoscopy is something of a buzz word in paediatric surgical circles at the moment. It contains five articles about laparoscopic surgery: three about cholecystectomy,[1–3] one about pyloromyotomy,[4] and one about untwisting a torsion of the uterine adnexa.[5]

Gallbladder disease in children is not common (see Archivist 1991:940) but not rare and workers in Montreal,[1] Washington DC, and Nashville, Tennessee[3] report a total of 13 laparoscopic cholecystectomies in children between the ages of 7 and 16 years. There were no complications and the children were less distressed postoperatively and recovered quicker.

A report from Limoges, France describes the treatment of 10 babies with pyloric stenosis using laparoscopic pyloromyotomy.[4] The operation was successful and without complications in all 10. The final article in the series is one from Israel reporting the use of laparoscopic surgery in a girl of 11 years with torsion of the uterine adnexa.[5]

An accompanying editorial discusses the advent of laparoscopic surgery (laparoscopic cholecystectomy in adults was first described in 1989) and lays emphasis on the need to ensure adequate training in these techniques and the potential for disaster in inexperienced hands.[6] Clearly any surgeon new to the technique should at first operate only under supervision. According to the team in Nashville it takes some 15 to 20 operations to become competent.

ARCHIVIST

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[†] A good title is worth imitating. Richard Hoggart's best known book, *The Uses of Literacy*, was published in 1957 and stays in the memory, I suspect, largely because of its title In fact, it was to have been called 'the abuses of literacy', but was changed because of the objections of a libel lawyer By the time I got round to reading it, it was way out of date and not very relevant I enjoyed the first part of his autobiography[7] though and am settling into the second[8], recommended reading for when you've finished the *Archives* and want a break from paediatrics.

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Archives of Disease in Childhood 1992, 67: 632–635

Height and body proportions in child abuse

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Abstract

Abused children are said to retain 'infantile body proportions'. The presenting height, sitting height, and leg length standard deviation scores of 91 victims have been calculated from data derived from a study of local inner city schoolchildren. In the study population 31/91 (34%) were significantly short and all but two of these had relatively shorter legs than backs, this limb disproportion being significant in 17. In 25 patients of the original group followed up after various social interventions there was a significant recovery of leg length. Measurement of height and proportionality, especially when compared with appropriate modern or local standards, is an important means of detecting and following up victims of child abuse.

The impact of child abuse on growth is well recognised,[1–4] and the victims are classically said to retain 'infantile body proportions', but this statement is largely based on anecdotal observations or small series.[5–7] The present study was designed to look at the height and body proportions of an unselected sequence of children presenting to one of the authors (LST) in whom subsequent social and medical investigation showed unequivocal evidence of physical abuse and/or neglect. Some of the data on the height and weight of these children as well as the relationship of these measurements to social class, developmental delay at presentation, and recovery towards normal with various types of social intervention have been previously published.[8–10] In the course of the study the previously noted limitations of the current UK standards for analysis of sitting height and leg length again became manifest,[11] necessitating the use of proportionality standards derived from a local study of inner city schoolchildren.[12]

Patients and methods

Ninety one children with good medical and social evidence of physical abuse and/or neglect had measurements of height, sitting height, and derivation of leg length made by a single professional auxologist in the measurement laboratory of the Sheffield Children's Hospital. A Harpenden stadiometer and sitting height table (Holtain) were used to measure the children; the reliability of measurement of a single child using this equipment, methodology, and auxologist has previously been published.[13 14]

In order to allow comparison of children of different ages and sex, a standard deviation (SD) score was calculated for each value using data derived from a study of 345 local children[12] to calculate sitting height and leg length SD score. Although the height standards derived from the Tanner and Whitehouse data are still broadly applicable to the current UK population, the 1978 data on sitting height and leg length[15] shows a major, relatively fixed, discrepancy when compared with present day populations in that children have longer legs and shorter backs than would be anticipated from the use of the Tanner and Whitehouse standards.[11 12] The local data on a relatively small population was used because of the similarities of social class and other demographic data to the abused group, but has been validated in a larger study of 2965 children with a broader population mix[16] and is also strikingly similar to modern European data.[17] In a normally distributed population the SD score will have a mean of zero and a SD of one. SD scores of −2 to +2 will include 95·44% of the population.

The group consisted of 52 boys and 39 girls with an age range of 0·2 to 13·2 years; the age distribution was appreciably skewed to the younger ages (median age 2·5 years), and the sex and age distribution reflects that of a previously published study by Baldwin and Oliver.[18]

The employment category of the parent(s) is shown in fig 1. Demographical information on the social class and unemployment rates (but not the single parent family rates), of the electoral wards in 1986 from which the normative local measurements were collected is available and shows a 19·5% unemployment rate and 25% of the population in social classes IV and V. There is therefore an apparent over representation of unemployed parents, even compared with high local rates, in the abuse

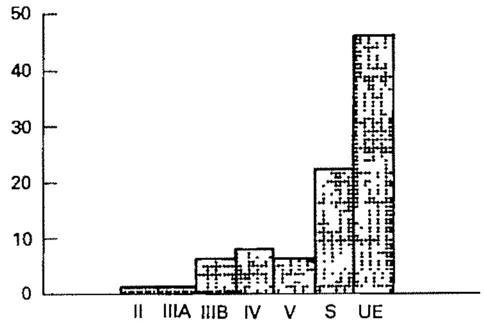

Figure 1 Employment category of the parent(s) of the abused children. (S, single parents; UE, unemployed)

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Accepted 1 January 1992

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group and also a very large number of single parents. This distribution has previously been described and discussed.[19 20]

As physical abuse may on occasion be a 'spur of the moment' event, and neglect by its very nature long term, the patients were subdivided into two groups, one of 57 children with physical abuse and another of 34 deprived children with no known physical injury, to determine if there was any difference in body habitus. In addition, 25 patients were seen for follow up measurements at one to four years after presentation.

Results

Figure 2 shows the results of a local study[12] measuring the height and sitting height of 345 children from inner city Sheffield superimposed on the current UK charts of Tanner and Whitehouse.[15] It can be seen that although there is a tendency for 'modern' children to be very slightly taller than their predecessors, a major discrepancy is seen in relation to body proportions, with the study group having consistently longer legs and shorter backs.

To analyse the data to show the effects of abuse on individuals, a scattergram of sitting height SD score has been plotted against leg length SD score as illustrated in fig 3. This means of demonstrating the data shows individuals with normal stature falling within the central stippled box. Furthermore, disproportion can be represented by the perpendicular distance from a 'line of perfect proportion' (where sitting height SD score=leg length SD score) drawn through the intercept.

Figure 4 shows that 31/91 abused or deprived children were found to be short ($p=<0\cdot001$); (17/57 and 14/34; 30 and 41% respectively (not significant) in the two subgroups). All but two of these children showed leg length disproportion. The significance disproportion can be estimated by the method described by Young *et*

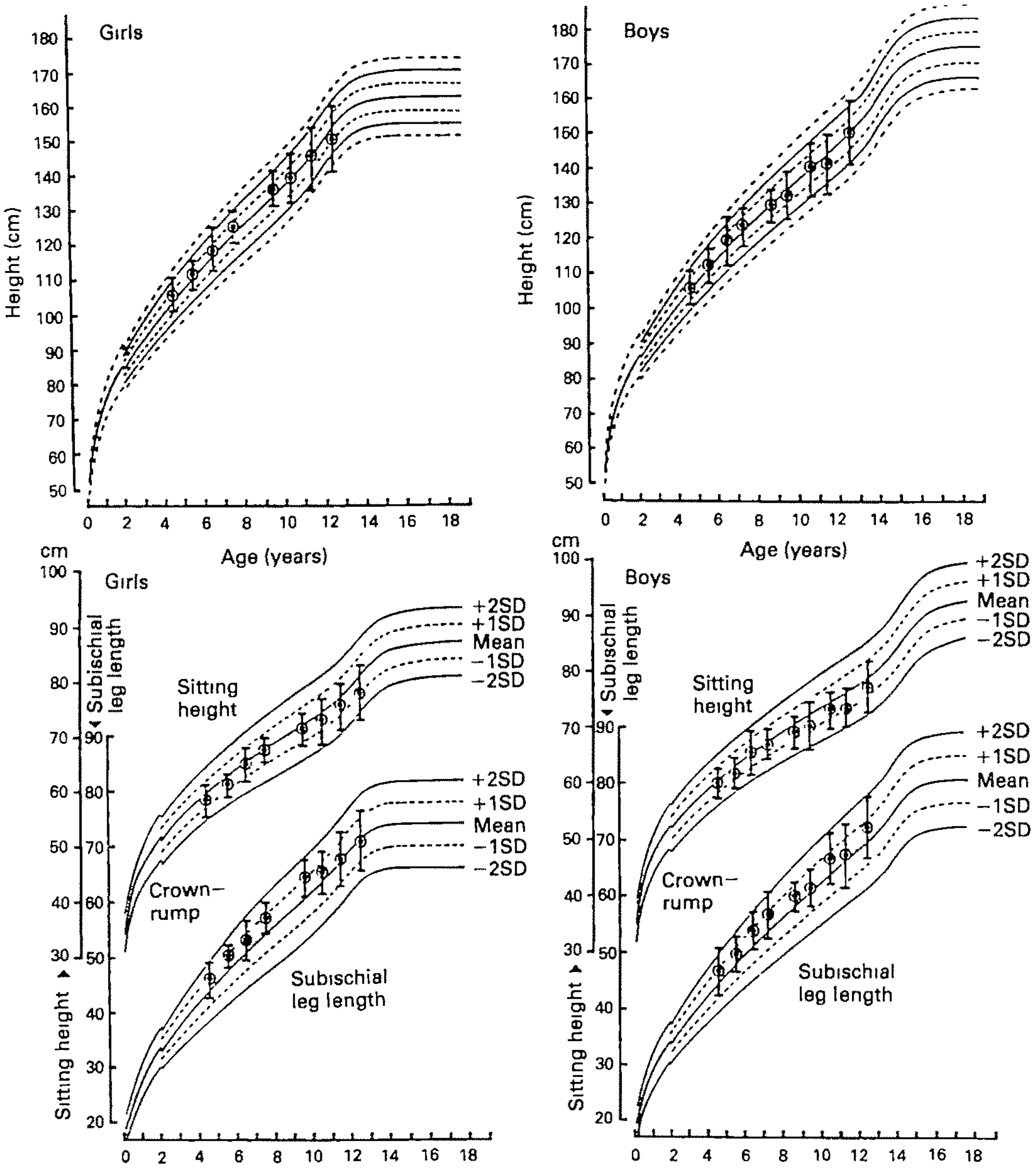

Figure 2 Mean (SD) heights, sitting heights, and subischial leg lengths of 345 inner city Sheffield schoolchildren plotted on conventional UK charts

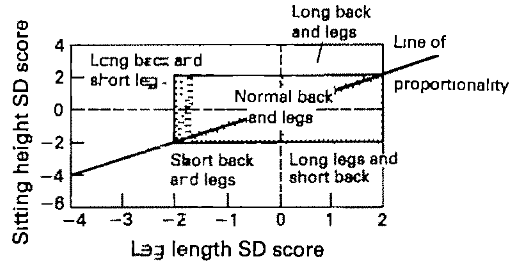

Figure 3 Demonstration of the scattergram used to represent the height and proportionality of individuals in the study.

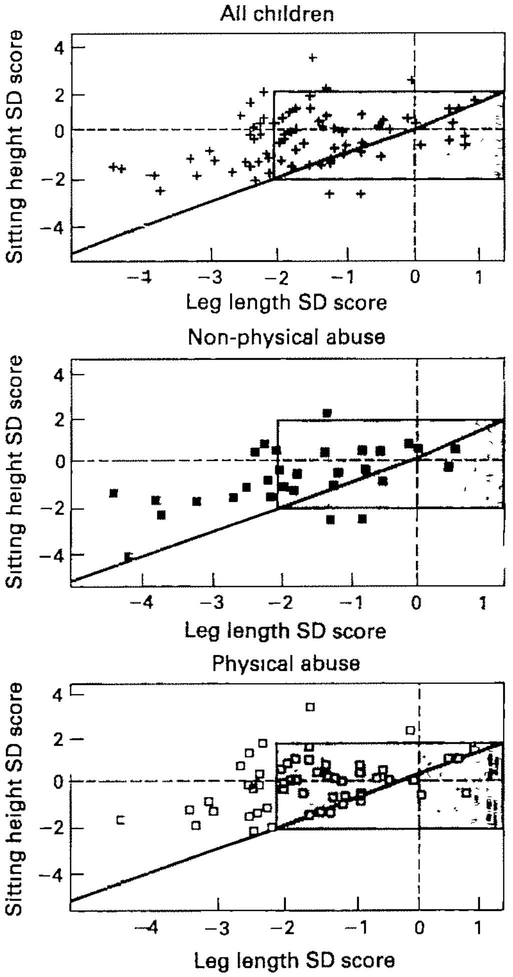

Figure 4 Scattergram of sitting height SD score against leg length SD score calculated from modern local data. Normal stature is encompassed in the central shaded area and the 'line of perfect proportion' is drawn through the intercept. Upper/lower segment disproportion is thus indicated by the perpendicular distance from this line.

al.[21] By subtracting the leg length SD score from the sitting height SD score, values of more than ±2 SD can be taken to represent statistically significant disproportion as shown in fig 5 where 17 children show significant shortening of the limbs compared with the back.

The group as a whole showed an appreciable skewing to the lower social classes and unemployed and single parents. This may represent a real phenomenon or a difference in ascertainment of cases but is probably a combination of both factors. Shorter leg length may in itself be associated with lower social class[22] and a secular increase of leg length occurs with improving social circumstances.[23] To exclude the difference in proportionality being due to social class effects, rather than being truly secondary to abuse, leg length SD score was related to three broad social categories (non-manual, n=8; manual, n=14; unemployed and single parent, n=69). Although the numbers in the higher social class groups were small there was a tendency for the shortest legs to be seen in the *higher* social class abused children (fig 6), making the observed disproportion unlikely to be due to social class effects alone.

The table shows the SD score at follow up in 25 patients (a mixture of the two subgroups), from one to five years after presentation and after a variety of social interventions, ranging from adoption and long term fostering to home care with social work supervision. There is a tendency for all values to 'recover' towards the mean, but this only reaches statistical significance for leg length. There was no apparent relationship between the initial degree of stunting and subsequent 'catch up' growth.

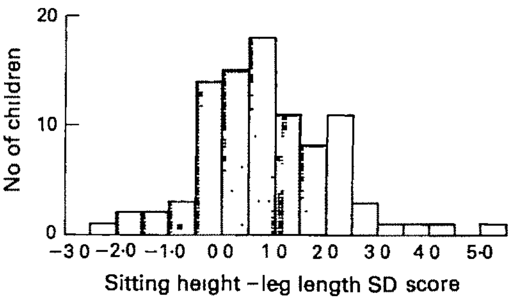

Figure 5 Leg length SD score subtracted from sitting height SD score. Significant disproportion is represented by the unshaded columns.

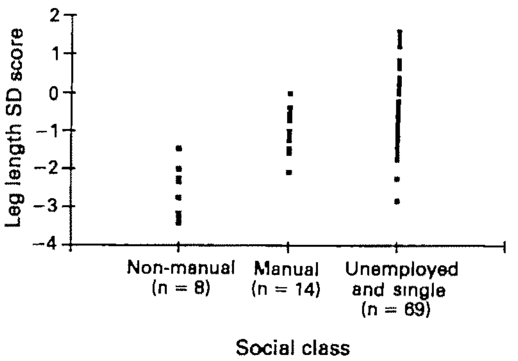

Figure 6 Leg length SD score plotted against three broad divisions of social class.

Height (Ht), sitting height (SH), and leg length (LL) SD scores at presentation and follow up (Ht2, SH2, LL2) of 25 children

	Range	*Mean*	*SD scores*
Ht	−4·3 to −0·1	−1·6	1·1
SH	−4·7 to +0·6	−1·5	1·2
LL	−3·4 to +0·3	−1·3	1·1
Ht2	−2·6 to −0·1	−1·2	0·8*
SH2	−2·9 to +0·7	−1·1	0·9†
LL2	−2·6 to +0·2	−0·9	0·7‡

*Ht *v* Ht2 p=0·07, †SH *v* SH2 p=0·09, ‡LL *v* LL2 p=0·035

Discussion

There can be no doubt that physical abuse and neglect of children leads to short stature and failure to thrive. The correlation of speech and developmental delay with shortness leads to the conclusion that both are manifestations of long term unhappiness and disruption within the family.[9] The short, abused, children will show a recovery of growth with the more radical changes in the home circumstances and this can be used to gauge the success of any intervention.[8] Children can also show catch-up growth from within the normal centile range to a higher centile channel on removal from the abnormal environment, demonstrating that they have not been achieving their full growth potential[10]; although growth screening programmes might lead to the identification of some cases of 'non-organic failure to grow', some children would escape detection.

We have demonstrated that a significant proportion of abused children are short and that lower limb disproportion is a frequent finding. As control of the growth of the long bones is largely mediated by growth hormone and growth hormone dependent growth factors, the lower leg stunting shown in these children, and the recovery with social work intervention, adds weight to the proposition that this poor growth is due to reversible undersecretion of growth hormone.[24–26] One could postulate that a combination of emotional and environmental factors, possibly with chronic sleep disturbance, act through the hypothalamus to decrease nocturnal growth hormone release. Suboptimal nutrition could also further modify growth factor action in the periphery.

Our thanks to Mrs M Pickering, auxologist, Dr D Skuse, Institute of Child Health, for his helpful comments and knowledge of the literature; and Mrs M Kessel, principal social worker, Sheffield Children's Hospital

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Archives of Disease in Childhood 1992; 67: 636–639

Home blood pressure monitoring in diabetes

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Abstract

Forty three children with diabetes were recruited to evaluate home blood pressure monitoring using an electronic oscillometric sphygmomanometer (Philips HP5330). This device was found to be simple to use and reliable. It fulfilled the accuracy criteria of the American Association for the Advancement of Medical Instrumentation for both systolic and diastolic blood pressure and those of the British Hypertension Society for systolic blood pressure. Thirty eight children successfully measured their own blood pressure at home and taught other family members to do the same. The results indicate that home blood pressure monitoring is of value in the management of diabetic children.

Diabetic nephropathy is the major life threatening complication of juvenile onset diabetes.[1] Preceding the nephropathy by as much as 10 years there may be a small but significant rise in blood pressure, usually together with microalbuminuria.[2] Antihypertensive therapy at this normotensive stage (according to the criteria of the World Health Organisation (WHO)[3]) can prevent the progressive decline in renal function and associated rise in blood pressure.[4] Blood pressure then, should be measured as accurately as possible in young diabetic patients.

When measured in outpatient clinics, blood pressure is often raised.[5] In adults, a series of pressure measurements at home is helpful in distinguishing patients with sustained hypertension from those with 'office hypertension'.[6] Home recordings using an electronic sphygmomanometer correlate closely with ambulatory measurements,[7] which have been shown to be of greater predictive value than office measurements.[8] The accurate assessment of blood pressure in young diabetics should therefore probably include a representative home series before appropriate diagnostic and therapeutic decisions can be made.

As familial hypertension may be a risk factor for nephropathy,[9] the blood pressure of parents and siblings should also be assessed; home monitoring would provide a practical means of doing this.

To our knowledge, home blood pressure monitoring in diabetic children and their families has not previously been evaluated. As the usefulness of such a technique depends primarily on the reliability and accuracy of the equipment when used in the population under review and on the abilities of those performing the home monitoring, this study was designed to examine these factors and to assess the potential value of home blood pressure monitoring.

Patients and methods

Forty three (26 male, 17 female) children and teenagers with insulin dependent diabetes were recruited randomly from the clinic over a six month period. Their mean age was 15·0 years (range 8·8–19·3 years) and mean duration of diabetes 6·7 years (range 0·2–17·3 years). The home monitor used was the Philips HP5330 which measures systolic and phase V diastolic blood pressure by the oscillometric method and displays the results digitally. The study initially validated the home monitor, and then examined the results of home blood pressure monitoring in these patients and some of their families.

VALIDATION OF THE HOME MONITOR

The validation procedure included the criteria of the American Association for the Advancement of Medical Instrumentation (AAMI)[10] and the British Hypertension Society (BHS) protocol.[11]

Pressure indicator accuracy and interdevice variability

Calibration was checked by connecting the monitor to a standard mercury column with a Y connector. The pressure recorded on the monitor was then compared with that indicated on the mercury column. This was done for pressures of 0, 50, 100, and 150 mm Hg before use and on return from each family for all of the eight monitors purchased for the study. The AAMI protocol requires 95% of measurements to be within 3 mm Hg of the reference standard. Interdevice variability was assessed by analysis of variance.

Device validation

The subjects rested in a sitting position for at least five minutes before their blood pressure was measured on the right arm using an adult cuff (bladder size 12×22 cm). No child was admitted to the study in whom this cuff size would have been inappropriate.[12] The blood pressure was measured simultaneously with the monitor and a random zero sphygmomanometer by using a Y connector. Two or three pairs of readings were recorded at two minute intervals. Systolic and diastolic (phase V) pressures were recorded by auscultation to the nearest 2 mm Hg.

The AAMI protocol requires the mean difference to be <5 mm Hg and the standard

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deviation (SD) to be ≤8 mm Hg for both systolic and diastolic pressures. The BHS protocol grades the monitor on the cumulative percentage of measurements differing from the reference sphygmomanometer by 5, 10, and 15 mm Hg.

Acceptability for home use

The patients were taught to use the home monitor and were asked to record their own blood pressure at home three times between 1730 and 2100 hours for three days. They were asked to rest in a sitting position for at least five minutes before starting and to leave at least two minutes between readings. The importance of correct positioning of the cuff around the right arm, correct inflation procedure,[13] a steady deflation rate of 2–3 mm Hg/second, and keeping the arm and tubing still during the measurements (as oscillometric devices can give inaccurate results with excessive movement) were all explained and reiterated in an instruction leaflet given out with the monitor. A chart was provided for recording the results with space for comments on the monitor. The patients were asked to teach the rest of the family how to use the device and record the results at home in a similar manner.

The monitor was collected from the home a week later. The participating family members were weighed and measured, asked details of illnesses, medication, and whether they had encountered any problems in using the monitor.

The mean value for systolic and diastolic pressures was calculated for each diabetic child and their natural mother, father, and eldest sibling (aged >10 years). Any measurement where either the systolic or the diastolic pressure was >30 mm Hg from the mean was rejected as invalid and the mean computed again from the remaining measurements. Any occasions on which it had been recorded that the monitor had failed to function were also noted as were any other comments written or verbal about the monitor. Unless at least three valid measurements were available the blood pressure series was not used for further analysis.

EVALUATION OF HOME BLOOD PRESSURE MONITORING

The mean of each diabetic child's blood pressure measurements that had been recorded using the home monitor in the clinic (when validating it against the random zero sphygmomanometer) was calculated and compared with the mean home blood pressure obtained with the same home monitor. The mean home blood pressure of the diabetic children and siblings was compared with the blood pressure centiles for height based on the data of Andre *et al*[14] as suggested by the BHS.[12] The mean home blood pressure of each parent was graded according to WHO criteria: normal (<140/90), borderline (between 140/90 and 160/85), and high (>160/85).[3]

Results

VALIDATION OF THE HOME MONITOR

Pressure indicator accuracy and interdevice variability

At all pressures compared (0, 50, 100, and 150 mm Hg), 100% monitor measurements were within 3 mm Hg of those indicated on the mercury column. Each monitor was used by between four and eight families and there was no deterioration in accuracy over the course of the study. Analysis of variance revealed no significant interdevice variability.

Device validation

A total of 124 paired measurements were recorded in 43 patients (three pairs of readings in 38 patients and two pairs in five patients). The range of systolic pressures in the 43 diabetic children was 75–157 mm Hg and the range of diastolic pressures was 43–98 mm Hg. The home monitor's systolic pressures fulfil the AAMI standard for accuracy (mean (SD) difference 1·7 (5·1) mm Hg) and achieve BHS grade B. The monitor's diastolic pressures fulfil the AAMI criteria (mean (SD) difference 4·9 (5·8) mm Hg), and achieve a BHS grade D. There was no statistical evidence of terminal digit preference in the random zero sphygmomanometer readings.

Acceptability for home use

None of the 43 patients invited to participate declined at the start of the study and 38 completed the home monitoring satisfactorily. Five failed to complete the home blood pressure series, but when asked to demonstrate whether they could use the monitor correctly, all were able to do so. A total of 69 natural parents (33 fathers, 36 mothers) and 27 eldest siblings (15 male, 12 female) also participated.

Rejected readings occurred in <2% of over 1100 home blood pressure measurements. These were usually very high systolic readings which tended to occur as a result of excessive movement during the procedure. Five participants noted when the monitor either failed to record (usually when the cuff deflation was too slow) or recorded 'error' (usually when cuff deflation was too fast). A total of 61% of participants produced nine measurements each, while the others produced between three and eight. Although most of these stated that they had not had sufficient time to do all three readings for three evenings as requested, some of these missing readings may have resulted from machine failures or faulty technique.

A few subjects complained that the cuff was uncomfortable. There were otherwise no reports of any significant problems and the majority of diabetic children and their families said that they had enjoyed participating in the study.

EVALUATION OF HOME BLOOD PRESSURE MONITORING

Only the results for systolic pressure were used in reviewing the blood pressure of the diabetics and their families.

Of the 38 diabetic children who completed the study, 66% had a mean home systolic pressure within 10 mm Hg of their mean clinic systolic pressure (fig 1). Three children had a clinic blood pressure more than 10 mm Hg

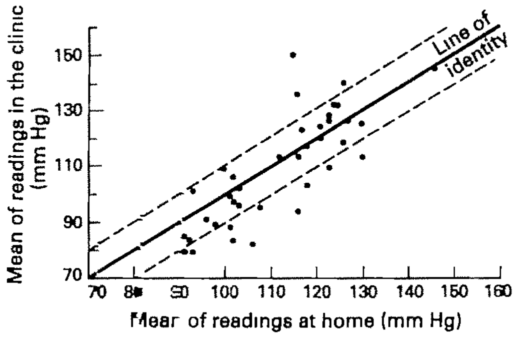

Figure 1 Comparison between the mean systolic blood pressure measured by the home monitor in the clinic and the mean systolic blood pressure at home.

above their mean home blood pressure, one differing by 33 mm Hg. Ten children had a home blood pressure more than 10 mm Hg higher than their clinic pressure.

One 17 year old diabetic boy had a mean systolic pressure of 145 mm Hg both in the clinic and at home; this was above the 90th centile for his height. His mother is a diabetic and her mean home systolic blood pressure was 134 mm Hg on antihypertensive treatment. One diabetic girl whose home blood pressure was on the 90th centile has a brother whose blood pressure was on the 97th centile and a father, aged 56 and non-obese, whose home systolic pressure was 168 mm Hg. The blood pressure of all the other diabetic children and their siblings was unremarkable (figs 2A and 2B).

Three fathers had a borderline raised systolic pressure (between 140 and 160 mm Hg) but the other members of their families were normotensive.

Discussion

This study successfully validated the use of the Philips HP5330 home sphygmomanometer in diabetic children and demonstrated the feasibility of home blood pressure monitoring in this group and their families.

Electronic sphygmomanometers designed for use in adults may not be sufficiently simple to use, reliable and accurate for use in children and teenagers. Some devices designed for self measurement of blood pressure fall far short of basic standards and some of the validation tests to which they have been subjected are also questionable.[10] [11] The detailed protocols of the AAMI and BHS address these problems and it is hoped that, in the future, home sphygmomanometers will be subjected to more rigorous validation procedures by the manufacturers before being put on the market. Meanwhile, by adapting a combination of those stringent tests to a paediatric setting, we have provided a model for further studies and have validated one home monitor for more regular use by the diabetics attending our clinic.

The home monitor was shown to be reliable in that all eight monitors maintained a high degree of pressure indicator accuracy throughout the study and did not significantly vary from each other. It passed the validation criteria for the AMI protocol and achieved a BHS grade B for systolic pressure (grade A has proved unobtainable by any device so far[9]), but performed less well for diastolic pressures. However, this does not invalidate its use, as measurement of diastolic pressure in children is notoriously difficult, inaccurate, and inconsistent.[14] [15] The random zero sphygmomanometer was used as the reference standard in preference to a standard mercury sphygmomanometer, although it was known that it slightly underestimates both systolic and diastolic pressures.[16] This was done to minimise observer bias and prevent digit preference since there was by necessity a single observer (CG).

Important features of the home monitor were that it was simple to use and seldom malfunctioned. Even those who failed to complete

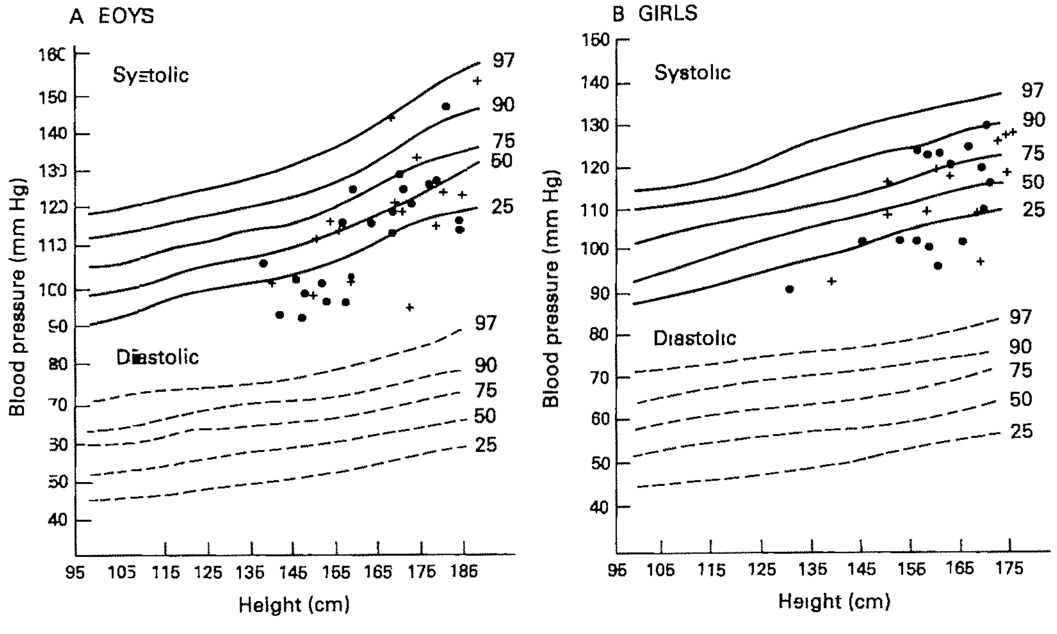

Figure 2 (A) Systolic blood pressure of diabetic boys (●) and their male siblings (+) plotted on centile charts for height.[14] (B) Systolic blood pressure of diabetic girls (●) and their female siblings (+) plotted on centile charts for height.[14]

the home blood pressure monitoring had understood after one demonstration how to use it correctly but were not sufficiently motivated to continue with the study. The majority of the diabetic children participated enthusiastically and also enlisted their families into the study with excellent results. The participants were asked to measure their blood pressure in the evenings rather than throughout the day to improve the acceptability of the study. As this is a time of day when blood pressure is relatively stable,[17] the home series was still felt to be representative of their day to day blood pressure.

The numbers of diabetic children, parents, and siblings involved in this study were small as it was a validation and feasibility exercise. However, the results clearly demonstrate the potential value of home blood pressure monitoring. It appears to distinguish office hypertension from sustained hypertension: the boy with a persistent systolic pressure of 145 mm Hg has since been further investigated and treated, whereas the girl with a clinic pressure of 150 mm Hg and a home pressure of 115 mm Hg has avoided unnecessary intervention.

The home monitor provides a profile of the family's blood pressure, so that diabetic children who are possibly at risk of hypertension can be followed more closely. Whether familial hypertension is an important risk factor in diabetic nephropathy requires further research. As many diabetic teenagers attend clinics unaccompanied, home monitoring is a practical method of assessing the blood pressure of their families and probably of more relevance than an occasional clinic measurement. It may also provide useful information for the general practitioner in the surveillance of families with a tendency to hypertension (the father with hypertension is now being treated). In fact, such family blood pressure studies should perhaps be done in conjunction with general practitioners, possibly using the diabetic liaison health visitor to teach and supervise the home monitoring.

It was surprising that 10 children had a home blood pressure higher than their clinic pressure. Although none of these was above the 90th centile, these home readings may be of greater prognostic significance than their clinic blood pressure, as has been demonstrated in adults.[8] Large prospective studies would be needed to answer this question.

We did not use a control group of non-diabetic families in this study but instead compared the blood pressure of the diabetic children and their siblings with centile charts which relate pressure to height. These are particularly useful in diabetic children in whom blood pressure and height are measured regularly. In any child whose blood pressure is in the upper centiles or whose pressure appears to be crossing centiles, a home series and family blood pressure profile may be appropriate.

In summary, the management of diabetic children includes the prevention of complications. Careful assessment of blood pressure is part of that surveillance and this study demonstrates that home monitoring is feasible and accurate. We believe it has great potential value in the management of diabetic children, particularly in distinguishing sustained from office hypertension, and in providing a blood pressure profile of a diabetic child's family.

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Incidence of normal micturition in myelomeningocele patients

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Accepted 7 January 1992

(*Arch Dis Child* 1992,67:640–1)

Abstract

Among 108 consecutive patients with myelomeningocele aged 5–12 years initially treated by a selective policy, seven (6·5%) achieved spontaneous urinary continence, five with normal micturition and two with urgency. All had positive conus reflexes and incomplete cord lesions which, with one exception, comprised motor as well as sensory sacral sparing.

Neuropathic bladder, with urinary incontinence and the risk of renal complications, is a major problem for patients with myelomeningocele and especially for those with smaller lesions whose handicaps otherwise tend to be slight. Reports of patients originally treated on a non-selective basis indicated normal urinary control in 23%[1] to 33%[2] of cases, including a few with thoracolumbar lesions. In a series of children initially managed selectively 51% were stated to be continent of urine.[3] Because myelomeningocele almost always involves the terminal spinal cord, these proportions seem surprising and we considered that this issue deserved re-examination.

Patients and methods

Casenotes were reviewed of all 108 surviving myelomeningocele patients treated at the Mersey Regional Neonatal Surgical Unit during the years 1979–85 inclusive. A selective treatment policy, employing Lorber's criteria,[4] had been practised during this period except in that a few neonates with thoracolumbar lesions had been actively managed at the parents' request. Surgical closure of the spinal lesions was undertaken neonatally.

Patients whose notes indicated normal urinary control, or did not exclude this possibilty, attended for review when details of their pattern of micturition were recorded and their spinal neurology was examined.

Results

One patient had been lost to follow up. Sixty five children were under the care of the urology department with a urodynamically proved neuropathic bladder and the notes of 31 others clearly indicated this diagnosis (15 had intermittent or indwelling urethral catheterisation, 10 had constant urinary leakage with the use of incontinence pads, five had urinary diversion, and one was dry due to regular bladder expression).

Among the 11 patients reviewed clinically, four had gross urinary and faecal incontinence. Five had an entirely normal pattern of micturition by day although one had primary nocturnal enuresis. Two children were fully continent but had marked urgency of micturition.

Neurological examination of the seven children with spontaneous daytime urinary continence showed a primary neurological level (that to which motor and sensory functions were entirely normal) ranging from L3 to S2. All had positive conus reflexes and an incomplete cord lesion which, except for one girl with urgent micturition, comprised motor as well as sensory sparing in the second to fourth sacral segments. None had suffered symptomatic urinary infections; recent ultrasound examinations or intravenous urography had shown normal upper renal tracts. Bowel habit was normal in all cases.

The incidence of spontaneous urinary continence in relation to the anatomical level of the cord lesion was thoracolumbar 0/8, lumbar 3/44 (7%), lumbosacral 3/39 (8%), and sacral 1/16 (6%).

Discussion

The incidence of spontaneous urinary continence in the present series, 6·5%, is far less than that previously claimed of children treated by non-selective[1 2] or selective[3] policies and lesser still when considering those with entirely normal daytime micturition.

Normal urinary control would be expected only of patients with positive conus reflexes and incomplete cord lesions with both motor and sensory sacral sparing, as were the findings in the present series. Incomplete cord lesions are quite common with sacral and lumbosacral myelomeningoceles but unusual with lumbar and exceptional with thoracolumbar lesions. As a rule there is only sensory sacral sparing and when this is accompanied by positive conus reflexes a precarious form of urinary control may be achieved but one which is undoubtedly abnormal.[5] Urgent micturition is associated with detrusor hyperreflexia and detrusor–sphincter dyssynergia; residual urine is common and upper renal tract complications may develop. A few patients with a combination of detrusor areflexia and moderate urethral resistance manage to stay more or less dry by regular voiding by abdominal straining or compression. Possibly previous reports included as having normal urinary control some patients precariously continent by these abnormal means, others where the casenotes were inaccurate and, perhaps, a few with pure meningoceles rather than myelomeningoceles.

Our findings have prognostic implications. Neonatally it is impossible to be certain of sacral motor sparing but conus reflexes are readily demonstrated and so also is sensory sparing by general arousal to perianal pinprick. No matter how slight the neurological deficit otherwise, neuropathic bladder is virtually certain in an infant with negative conus reflexes or a sensory complete cord lesion. By contrast, one with a combination of positive conus reflexes and a sensory incomplete cord lesion *may* ultimately prove to have normal bladder and bowel control.

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Treatment of refractory ulcerative oesophagitis with omeprazole

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Accepted 14 October 1991
(*Arch Dis Child* 1992;67:641–2)

Abstract

A 7 year old boy with ulcerative oesophagitis failed to respond to a two month course of intensive medical treatment using H_2 receptor antagonist treatment in combination with domperidone and sucralfate. He demonstrated complete resolution using omeprazole 10 mg once a day for eight weeks.

The aetiology of reflux oesophagitis is multifactorial. However, patients do have more frequent reflux episodes and poorer oesophageal acid clearance than normal individuals.[1] Conventional medical management of oesophagitis in childhood is based on positioning and the use of pharmacological agents including H_2 receptor antagonist treatment. Although the usual clinical outcome is effective resolution of symptoms, a proportion of patients with severe oesophagitis fail to respond. Omeprazole as an alternative treatment to H_2 receptor antagonists has been extensively reported in adults with ulcerative oesophagitis and peptic ulcer disease,[2] but not in children.

Case report

A 7 year old boy presented with vomiting associated with postprandial colicky abdominal pain and a weight loss of 4 kg in the preceding six weeks. There was a history of effortless vomiting from birth, which had not previously been investigated. Despite this, growth parameters were appropriate for age: weight 23·5 kg (50th centile), height 119·5 cm (50th centile), and clinical examination was unremarkable but for borborygmi and non-specific abdominal discomfort.

A blood film suggested a mild iron deficiency anaemia with a haemoglobin concentration of 108 g/l, mean corpuscular volume 68 fl (normal range 7–95) and mean corpuscular haemoglobin 23 pg (25–30). Abdominal ultrasound and a barium meal and follow through were normal. Liver function tests, serum electrolyte concentrations, amylase and lipase, and urine and faeces microscopy and culture were also normal. Oesophageal manometry was not performed.

OESOPHAGEAL PH PROFILE

Oesophageal pH was evaluated using a pH sensitive antimony electrode introduced via the nares, and positioned 4 cm above the lower oesophageal sphincter under fluoroscopic control. Normal activity was allowed for the period of study (24 hours), and data were recorded on a solid state recorder and analysed using a computer programme (Grant Instruments (Cambridge) Ltd, Squirrel Meter/logger).

When compared with normal data taken from the work of Sondheimer and Haase,[3] the results demonstrated significant and abnormal gastro-oesophageal reflux. The lower oesophageal pH was pH<4 for 33% of the time compared with a mean (SEM) normal of 3·2 (0·6)%. There were 1·5 reflux episodes/hour compared with 0·84 (0·11), and the longest episode of pH <4 was 64 minutes compared with 31·6 (18·9).

UPPER GASTROINTESTINAL ENDOSCOPY

Upper gastrointestinal endoscopy showed circumferential ulceration and exudate in the lower third of the oesophagus. The stomach and duodenum were normal. The symptoms and oesophageal appearance did not resolve with a 12 week course of ranitidine (75 mg twice a day), together with domperidone (10 mg three times a day), and sucralfate (500 mg twice a day) (fig 1a). Omeprazole 10 mg once a day was

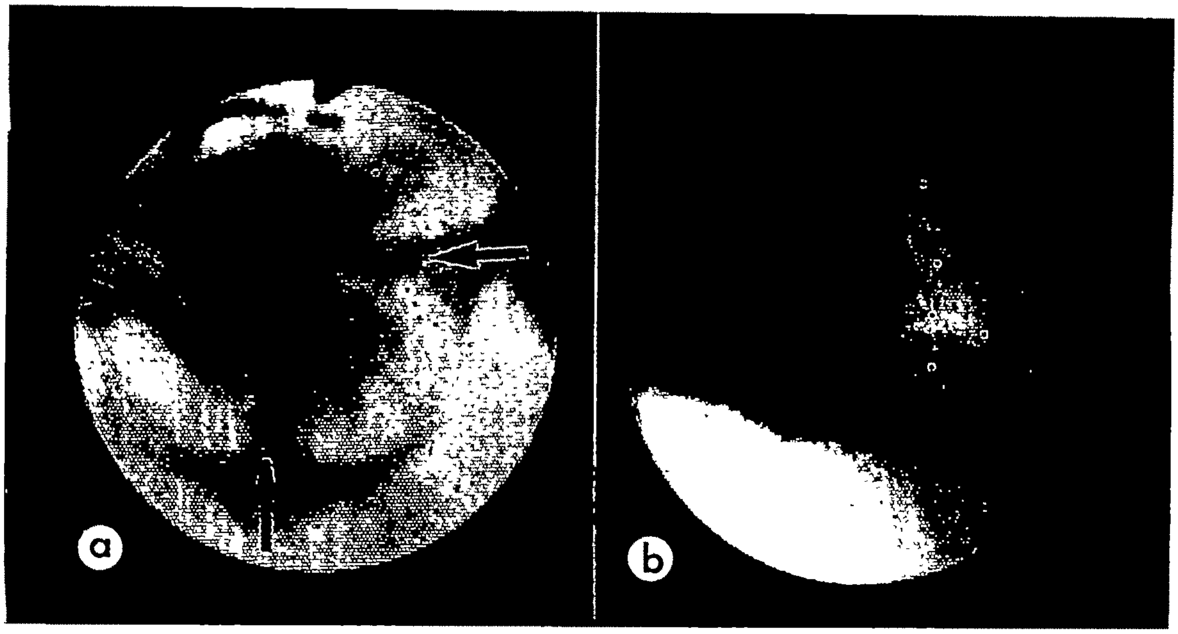

Figure 1 Lower oesophageal lumen (a) before and (b) after omeprazole treatment

started, and the patient gained symptomatic relief within three days, and demonstrated progressive weight gain. The abnormal endoscopic findings had resolved after eight weeks of treatment (fig 1b). At follow up one year later the child was asymptomatic.

HISTOLOGY

Histology of biopsy samples taken before the commencement of omeprazole treatment showed extensive ulceration with mixed fibrinous and inflammatory cell exudate covering a granulation base (fig 2a). Histology from biopsy samples taken after eight weeks of omeprazole treatment showed structurally normal oesophageal lining epithelium into which there was migration of only very occasional leucocytes (fig 2b).

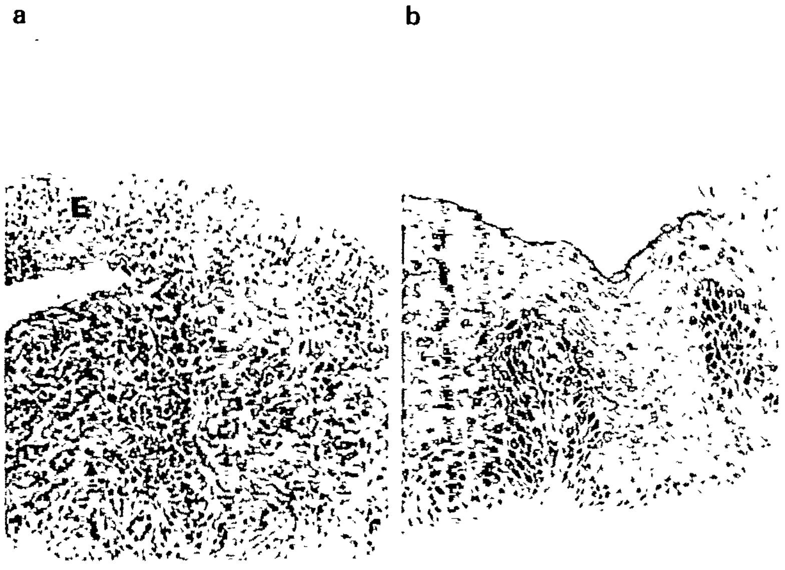

Figure 2 Oesophageal biopsy specimens (a) before omeprazole treatment showing inflammatory exudate (E) covering ulcer base. (b) After omeprazole treatment showing essentially normal oesophageal lining (Haematoxylin and eosin stain ×128.)

Discussion

We have documented ulcerative oesophagitis in a 7 year old boy with significant gastro-oesophageal reflux. Treatment with an H_2 receptor antagonist in combination with a promotility agent and mucosal protective agent for eight weeks failed to produce any improvement. The hydrogen-potassium ATPase proton pump inhibitor, omeprazole, produced symptomatic relief within three days and effective resolution of the oesophageal lesion after eight weeks of treatment. While there is no published experience of omeprazole use in children, it is the treatment of choice for severe oesophageal ulcerative disease in adults, and is more effective in treating reflux oesophagitis than H_2 receptor antagonist therapy.[4] It has been used safely at doses in excess of 60 mg/day for three years or more in patients with Zollinger-Ellison syndrome.[5]

Long term treatment using omeprazole is uncharted territory. While there will always be a place for surgery in severe gastro-oesophageal reflux disease, with or without oesophagitis or stricture,[6] we suggest that omeprazole should be considered as alternative treatment for children with ulcerative oesophagitis resistant to traditional therapy.

Dr Dalzell was the recipient of a Royal Children's Hospital Foundation Fellowship

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TYPES OF PSYCHIATRIC TREATMENT

Change the family, change the child?

Christopher Dare

This is the fourth of a series of articles on treatment of child psychiatric disorders.

The psychological health and the normal course of development of a child are closely determined by the nature of the security, predictability, and appropriateness of the immediate social environment. For most children, in Western postindustrial culture, this environment centres upon the nuclear family. Over the last four decades there has evolved a psychotherapeutic intervention that takes family life as its subject matter. This is now known, simply, as family therapy.[*] In its earlier stages it was designated whole family therapy or family group therapy.

Application of family therapy

Family therapy has become a widespread clinical practice within child and adolescent psychiatry. The research basis for this extensive application is slim, as is the case for most psychotherapeutic methods. There are also problems in the interpretation of the research: 'In sum, the search for an assessment of family therapy effectiveness has been frustrated by a research base that past reviewers have found difficult to synthesize'.[1] Hence, the justification for the use of family therapy in child psychiatric settings is largely based on 'clinical experience'[†]: it appears sensible to approach problems of behaviour and effective disturbance through the family context. None the less, in reviewing evidence for the efficacy of family therapy, Gurman and Kniskern report that the usefulness of family therapy is established for behavioural and emotional disturbance in childhood and adolescence.[2] Likewise, in the review of Hazelrigg *et al* there is a conclusion, from a meta-analytic study of a number of control trials of family therapy, that it can be shown to be more effective than no treatment or control treatments.[1] Most of the effective treatments reported by these authors, where the presenting problem is described, concern children with behaviour problems. Patterson has reported extensively on the effectiveness of his form of family intervention, based on social learning theory in behavioural disorder in primary school aged children.[3] Alexander and Barton showed the effectiveness of another form of family therapy (using an admixture of systems and behavioural theory) in the management of behavioural disturbed children.[4] Lask and Matthews have shown the usefulness of family therapy as an adjunct to physical treatments in asthma.[5] (The therapy here was 'structural' in form.) Ro-Trock *et al* have shown that family therapy added to the milieu treatments in an adolescent unit improves the benefits of the inpatient regimen.[6] In our own studies at the Institute of Psychiatry we have shown that family therapy is superior to a supportive individual therapy in the management of anorexia in adolescence.[7] [8] Our as yet unpublished findings demonstrate that the benefits of family therapy, in comparison to the control treatment, persists at five year follow up. Our family therapy can be designated as including psychoanalytic as well as structural and strategic elements.[9]

In addition to family therapy being used in the management of a child's presenting problems, it has also been used to alleviate family distress and to optimise family functioning in chronic physical illness.[10] In principle family therapy is to be considered as part of the treatment plan in a wide range of chronic and distressing childhood illness.

In the course of this introduction, defining labels have been attached to reported outcome studies. This is necessary as there are many forms of family therapy. Although there have been very few studies of the specific strengths and applications of the different schools of family therapy, it is necessary to describe them in order to understand the diversity of techniques used within the therapy. Examination of the origins of family therapy and the context in which it developed provides a way of defining the different theoretical origins and styles of current practice.

Origins of family therapy

Family therapy grew from dissatisfaction with the psychotherapeutic techniques that were available in the 1950s.[11] In the early 1950s therapeutic techniques of psychoanalytic psychotherapy and psychodynamic casework were, essentially, the only well established treatment methods in child psychiatry departments and in child guidance clinics. These techniques came to be addressed to the child and to the two parents, so that in a well staffed clinic three professionals were involved in the

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[*] Throughout this paper the word family refers to the household of a family of creation That is to say, it consists of a parent or parents with children for whom the adults are responsible for the foreseeable future Other members of the household related or unrelated by blood may be included in a therapy session

[†] Gurman and Kniskern point out that the efficacy of family therapy is best established in the form of marital therapy for marital problems.[2] Clearly, many children are seriously troubled by parental discord and marital therapy is not, therefore, irrelevant to child health professionals However, any discussion of marital therapy is beyond the range of this paper

treatment of one case. Such treatments, usually long term, if carried out conscientiously led to the discovery that other children in the family than the first one to be presented, had psychological difficulties. A fourth or even a fifth therapist might be recruited to the management of what had been, in the first instance, one case. Three problems arose: first, this technical development of multiple therapists was hopelessly uneconomic. Second, there were difficulties in coordinating the different therapies. Third, the unavailability of most child mental health problems to such intensive therapy was obvious as family resistance to long term psychotherapy became apparent.[12]

Family therapy began to be applied pragmatically to children's problems in the decade after the second world war.[13–15] The concepts and techniques largely resembled a psychodynamic group therapy with some psychodrama (in the therapies of Ackerman).

However another context, derived from the second world war, had a unique and crucial influence. The Veterans Administration (VA) was responsible for the health care of the former conscripts into the US armed forces. Given the age group and numbers of men recruited into the forces, and the stresses that they endured, it was unsurprising that, in the postwar period, the VA found itself looking after a large number of young men with psychotic illnesses which were, at that time largely untreatable. Modern psychopharmacological agents were unavailable and a few heroic experiments in the psychotherapy of these patients were yielding poor results. The National Institute of Mental Health (NIMH) and the VA set up research programmes investigating the families of young adult schizophrenic patients. The NIMH research[16] and the VA group both had long term effects not upon the development of a family therapy effective in the management of schizophrenia, but upon the conceptual framework and practices of the family therapy in child mental health settings.[17 18] Both groups observed processes within the family as a whole. The NIMH used psychological tests on all family members (the thematic apperception test, a projective test akin to the Rohrshach ink blots) and identified discrepancies between verbal meaning and the affective implications of communication in families ('pseudomutality' and 'pseudohostility'). The Pal Alto group looked at the family as it sat talking together with a member of the research team. The VA group was remarkable in that it drew upon unusual talents: Jay Haley, a communications expert; Geoffrey Bateson, a cultural anthropologist; Virginia Satir, a social case worker; and Don Jackson, a psychoanalyst, a follower of the American founder of 'interpersonal' psychoanalysis Harry Stacks Sullivan. All of these made distinctive contributions that have shaped modern family therapy. For example, Haley as a communications expert was specifically interested in the patterns of verbal and nonverbal communication. Bateson from previous anthropological field studies had experience of the discrepancy between overt and covert communication and its effects upon social behaviour.[19] Jackson was skilled in construing the nature of the psychological effects of one family upon each other and in mobilising psychotherapeutic interventions that addressed these effects. Satir drew upon knowledge of family and group processes observed in social work practice. The well known but inaccurately understood 'double bind' form of communication summarised some of the group's views.[20]

Family systems theory and family therapy

However the distinctive contribution of the Pal Alto research group derived from the introduction of systems theory[21] and ecology[22] into an understanding of families. The family members' mutual dependence and influence upon each other was seen to create a system that had properties in its own right and which were not necessarily predictable from the qualities of the individuals ('the whole is greater than the sum of the individual parts'). This concept, that the family could be defined as a totality, had a momentous effect upon the development of family therapy, far beyond the potential usefulness of family therapy in the management of schizophrenia in young adults. It has become incorporated as a 'family systems theory' approach. The Pal Alto group dispersed (after the early death of Jackson) but came to influence family therapy turning it from a marginal activity of a small group of child mental health workers to a major movement in contemporary thinking about families and children.

The family therapy movement has become synonymous with the concepts of family systems theory. As such it has had a large impact on child and adolescent psychiatric practice and is beginning to influence studies of child development[23 24] and on the scientific study of interpersonal relations.[25]

Family therapy techniques and practice

Despite the percolation of family systems thinking into empirical studies, family therapy remains, like much of psychotherapy, a practice driven by clinical observation and experience rather than by scientific studies. Despite the fact that systematic reports of treatment trials[7] and of family systems investigations[26] are occurring, the description of most family therapy practice rely upon accounts derived from clinical know how. Contemporary family therapy can be described under the headings of 'schools' of practice.

Strategic family therapy

The roots of much modern psychotherapy lie in psychoanalysis with its tradition of listening, non-directiveness, and a belief in the therapeutic potency of insight promoting interpretation. The growth of other psychological treatments based on empirical psychology, especially learning theory, challenged these tenets of psychoanalysis. However, even before behaviour therapy had become well known, Haley as a family therapist (1963) had proposed that psychotherapy could be directive and goal orientated and he coined the phrase 'strategic' therapy.[11] What he meant by this was that the therapist had a responsibility to identify the end point of treatment, which should then be sought by whatever means. The viewpoint tends to be associated with a mistrust of theory based treatment goals and takes the problem as presented by the patient or the family consensus as the principle guide to the direction of treatment. Hence if the family nominate the child's faecal soiling as the problem then the therapist helps the family devise strategies to eliminate the soiling. The problem as stated *is* the problem, not a putative underlying psychopathology of the individual or of the family. This particular approach to therapy has been definitively described by Haley[27] and it characterises most therapies, especially those that are short term. It is especially relevant to work with young children and with acute problems. Almost any technique that can produce change can be called upon in the pursuit of a potent strategy to augment the power of the family over the problem. For example behavioural therapy techniques (especially the keeping of a diary of the unwanted and wanted behaviours), quasihypnotic suggestion, challenging interpretations and so on, may all be used. Some of the most striking methods are labelled as paradoxical interventions. The therapist raises the family's anxiety by suggesting that the symptom may have to get worse, remain indefinitely, or be deliberately enacted. Commonly a persuasive rationale for the suggestion may be given. Such techniques may have an effect by increasing the family's determination to counteract the problem or its effects. Likewise, the child with the symptom may be helped to feel more in control of the problem when instructed to perform the symptomatic behaviour deliberately. For example, an enuretic child may be advised to wet the bed deliberately ('You choose a time when the flood can be best dealt with'). Or the whole family might be encouraged to take on a symptom: a tic, nervous cough, or whatever. The use of strategic techniques, like all family therapy, is embedded within an approach to the family that is positive, supportive, and non-critical. The therapist tries to put the family into a frame of mind that they will be able to take charge of the symptom, if not immediately, in the longer term.

Structural family therapy

The great achievement of the Pal Alto group had been to produce a language whereby the space *between* the family members was attended to as much as to processes *within* the individuals themselves. That is to say the family was described as a whole, as an organisation with identifiable rules and structure. A family can be defined as existing to provide psychological support, companionship, and fulfilment to the adults (if there is more than one parent in the family) and to nurture children from infancy to young adulthood. To achieve these there must be systems of communication, of control, of nurturance, and of affect management. There have to be rules governing the balance of selfish and altruistic behaviour as well as establishing the demands of intimacy and separateness. Family members have different roles usually determined, in part, by age, gender, state of physical and psychological health, and by family traditions. A family has implicitly a definition of who is inside and who outside the family and of maintaining the distinction between the two areas. All of these aspects are especially important in inducing children into membership of the family and contribute significantly to the personality of the growing child. As these areas are examined and specified for different families the structure of a particular family is being described.

All family therapy, by definition, attempts to change the structure of the family but a particular group of family therapists has taken such change as its specific aim. This school centres around the teaching of Salvador Minuchin especially that emanating from the Philadelphia child guidance clinic.[28 29] Minuchin was most interested in the hierarchical structure of families, in the coalitions between family members, in the clarity or otherwise of its rules and controls, and in the clarity or otherwise of the boundaries between individual family members. In the form of family therapy associated with Minuchin, the therapist contrues a symptom as being an expression of a disorder of family organisation. Society and individual needs are taken to be best met by families with an optimal organisation. If that organisation does not pertain, dysfunction in the family can be said to occur and disturbance ensues in the individual. The therapy in seeking to identify and reverse family dysfunction facilitates the relief of the individual bearing the symptom.

Stated in this simplified way there are obvious dangers to structural family therapy in seeking to define socially determined organisations as 'normal' and the reverse as 'abnormal'. The main thrust of much structural family therapy is to clarify and enhance parental authority over the children, to strengthen the marital couple in their rule setting, and to make the children more separate from and subject to the parents. The structural therapist functions by adding professional authority to that of the parents. Instructions and directions are given to the parents as to how they should conduct family life with more clarity of organisation. Tasks are prescribed that in their completion, between sessions, will continue to augment the precision of family rules and to give the family practice in their maintenance. Such activities are manifestly beneficial, if successful, in chaotic and under-organised families.[30] Such structurally based interventions are also sensible in families where there is an apparent ideology of democracy that leaves children confused as to what are the differences between children and adults and what are the rules expected of them inside and outside of the family. Most families lie away from the extremes of chaos and ill placed democracy but none the less the techniques of structural therapy are widely applicable. A 'family diagnosis' will always attend to enduring structural qualities.

Behavioural family therapy

Many family therapists, as has been made clear in the descriptions so far, are directed towards explicit behaviours and, as such, have implicitly accepted the underlying principles of behaviour therapy. Some family therapists have made a wholehearted adaptation of behavioural practices to whole family intervention.[3 31] Such an approach will clearly be akin to aspects of the strategic, problem solving approach in that the unwanted behaviour will be accepted as the problem. A very detailed behavioural analysis will be made, the pattern of antecedent and subsequent events will be carefully investigated, and the frequency and timing of the problem behaviours identified by, for example, a diary. The symptom is attacked, directly, by alteration of the behavioural contingencies; the family is taught to ignore unwanted behaviour and to reward wanted alternatives systematically and enthusiastically.

Such an approach can be highly effective with troublesome misbehaviour, especially in young children. However the effectiveness of such an approach extends beyond simple behavioural management. Many children presenting with problems ranging as widely conduct disorder, depression, somatic disorders, or phobias may have poor self esteem. This can be continually reinforced both by the manifestations of the child's disturbance but also by the parents' sense of failure and helplessness consequent on their child's difficulties. It is easy for families to get into a cycle of blame and recrimination and the implementation of a simple behavioural programme as described can alter the family atmosphere. The parents and other children are directed to be positive and approving of what is acceptable while ignoring the negative and unacceptable.

Falloon has used behavioural notions of social skills and problem solving to help families with a schizophrenic member.[31] Epstein and Bishop have elaborated a programme, the McMaster's model, that likewise uses a great deal of direct behavioural instruction to change identified areas of apparent family dysfunction as well as individual misbehaviour.[32]

Transgenerational family therapy

So far the emphasis has been upon techniques that are widely used in family therapy and that are distinct from the mainstream of psychodynamic psychotherapy that dominates individual therapy It can be argued that these differences are more apparent than real,[9 33 34] but in the description of family therapy given so far the emphasis has been upon the family as an organisation that is defined by its transactional qualities: by those qualities that are directly observable or construable from the current pattern of interaction between family members. However, a family also has a history. The parent (or parents) has experienced family life during childhood and will draw upon those experiences in forming a new family. A child's experiences of nurturance and the formation of attachments will come into play, when the child is now adult, in the pattern of bonding and loving in the new family.[35] Bowen,[36] Framo,[37] and Byng-Hall[38] have described a variety of techniques whereby the family therapist calls upon the history of the family in order to gain therapeutic power. The tool of the transgenerational family therapist is the construction and examination of a family tree (also known as a geneogram). In this process each family member is asked to cooperate in the actual drawing of a family tree. Often it is most advantageous to ask the least involved, disengaged family member to tell of the present family and its forebears. Likewise it may be sensible to ask designated patients, the 'naughty' children about the family story so that they can show their affiliation by their knowledge and interest in that story. As the family members tell the therapist about who makes up the family and its genealogy, questions about the personality and relationships as perceived around that individual can be discussed. Different viewpoints illustrate generational and gender perspectives and allow the therapist to endorse both the sense of family membership, of loyalty, and of the normality of difference. The technique of drawing up a family tree is akin to psychodynamic work because it allows for the interpretation of rules, of patterns, of unconscious, and conscious identifications and so on. At the same time, the manner in which the therapist addresses the family can support and strengthen the family's hierarchical strength and intergenerational boundaries and so 'structural' work can be done.

Milan systems family therapy

Most of the techniques described so far have required the therapist to be rather active, to give strong direction to the therapy, and to invite the family to change by doing things differently. Such a style of therapy is most obviously appropriate for short term treatments, for those brought about by urgent problems, and for those cases in which the presenting problem is the management of misbehaviour in children. There are other situations, in which the therapy must be more reflective, exploratory, and more ambiguous in its ostensible aims. There are also therapists whose personal style tends more in these directions. Such a style resembles more the practice of psychoanalytic psychotherapy and it is not surprising that a form of family therapy embodying some of these qualities has evolved. What is less predictable is that this school has been extremely influential throughout the field of family therapy. This school was initiated by the Italian psychiatrist/psychotherapist, Mara Selvini Palazzoli. Because she worked and taught in Milan and because early in her move from individual to family therapy she was strongly influenced by Bateson, her school has become known as that of Milan systems therapy. Selvini-Palazzoli has outlined the development of her theory[39] and her coworkers and followers have written extensively on the methods of what has now become a worldwide school.

The Milan systems therapist does not seek to produce change by deliberately directing or restructuring the family. Instead the therapist tries to evolve an analysis of the family's history and relationship patterns by asking a series of questions that invite the family to reflect on their own and each other's experiences of their lives together. The aim is to expose the assumptions that underlie the attitudes and behaviour patterns of the family. This exposure, when successfully facilitated, leads the family itself to attempt new ways of relating to and treating each other without direct suggestions coming from the therapist. In passing, it can be noted that many of the interpretations that Milan systems therapists use to understand families are *transgenerational*, emphasising, for example, the rigid loyalty that families may show in adhering to particular patterns that determine the family organisation.

Common themes in family therapy practice

In the development of family therapy the designation of distinctive schools has been important in helping different ideas to be pursued rigorously and extensively but it has also led to counterproductive notions of orthodoxies and to competitiveness. Although the distinctive schools persist, the average practitioner will use a mixture of ideas and techniques derived from a variety of schools. Nichols, among others, has propounded the view that the different schools of family therapy share more than their adherents sometimes acknowledge.[40] The mixture that forms a particular therapist's style will depend upon the training, reading, and personal qualities of the therapist. There are regular themes in these eclectic therapies. In principle, all family therapy aspires to change family structures, respects hierarchical organisations and the differing needs of children and adults. All family therapies accept that the family will need to be engaged by a discussion of what they perceive to be the problem. Most family therapists accept that patterns of family functioning are transmitted from one generation to another resulting in what can be called a *family culture*. All family therapists will observe ethnocultural sensibilities.

Concept of the family life cycle

One particular concept shared by most family therapists is that a family is an evolving, growing structure going through distinctive stages with transitions denoting the move from one phase to another. This is the basis for the concept of the *family life cycle*, a major theme in all family therapy and relevant to any practitioner wishing to consider the family of a child.[33 41] The main implication of the concept is that at different phases of the evolution of a particular family there are likely to be characteristic tasks and preoccupations. For example, the family can be said to begin when a couple chose, or have forced upon them, the necessity to accommodate a child. The couple is a two person organisation, principally involved in the creation of a mutually supportive and enhancing personal relationship. The arrival of a baby demands a family unit organised around the need to maintain the biological integrity and healthy development of an infant. The couple's need as a pair takes second place. The pace of family adaptation becomes dominated by the changing needs for protection and nurturance of the infant growing from babyhood to the school child. At the point of entrance to whole time education there begins a period when, although child care remains a dominant activity, the parents' attention to their own interests and ambition can increase. The school age child changes as he or she matures, contributing a share to the changing needs of the family, and this process is accelerated as adolescence is reached and the potential for adulthood is signalled in the child. This requires further family adaptation and offers the possibility of more freedom for the parents. However, in childhood, the pace of change in the family tends to be dominated by the rate of development of children. The life cycle does not come to a halt in adulthood. The changes of midlife and of old age impinge on families, especially for young families, in the lives of the grandparents. The greater the number of people in the family going through major life cycle transitions, the greater the demand for change is imposed on the family as a whole. These demands for change are potentially stressful and family therapy can be seen as centering around the process of acquisition of skills to overcome these stresses.

Conclusion

All clinicians working with children will know the importance of the family's influence in determining the care of children and the management of their psychosocial life. Common sense, both social and clinical, will enable most problems to be handled by most of us. However, from time to time, common sense is of no use and then uncommon solutions are necessary. That is often the case where there are psychological problems in childhood whether arising *ab initio* or deriving from other difficulties such as chronic illness. Family therapy has some of the qualities of uncommon sense: convening a whole family meeting to discover solutions to problems does not come naturally to professionals or to patients. However many of the techniques of family therapy make clinically cogent and are powerful influences on family behaviour. These powers can be harnessed for the good of children in our professional care.

The author's research described in this paper has been generously supported by the Medical Research Council of Great Britain

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Archives of Disease in Childhood 1992; 67: 649–653

CURRENT TOPIC

Intravenous volume replacement: which fluid and why?

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Fluids available for intravenous volume replacement may be either crystalloid or colloid. The fundamental differences between these fluids are their effects on the Starling equation (table 1) which describes fluid flux between the intravascular and interstitial spaces. Starling stated that the rate of fluid movement into or out of a capillary is related to the net hydrostatic pressure minus the net colloid osmotic pressure.[1] The Starling equation has been modified to include coefficients which represent the permeability of the capillary membrane to small solutes (K_{fc}) and its ability to prevent large molecules such as plasma proteins from crossing it (σ_c).[2] Colloids may be used to replenish the oncotic strength of the blood, thereby enhancing its water retaining capacity.

Crystalloid versus colloid controversy

Colloids are widely used in Europe for volume replacement, while crystalloids are the fluids of choice in many centres in the USA,[3] but the relative merits of the two methods of management remain controversial.[4 5]

Workers in favour of colloids insist that the intravascular colloid osmotic pressure must be kept either above the capillary hydrostatic pressure or at least greater than 10 mm Hg in critically ill patients to avoid a poor prognosis.[6 7] Proponents of crystalloids maintain that colloids leak out of the capillaries, increasing interstitial colloid osmotic pressure which has a detrimental effect by increasing fluid flux out of the capillary.[8] This is more likely to occur if σ_c is reduced, as happens after burns, severe sepsis, and cardiopulmonary bypass.[9]

Colloid solutions expand the intravascular space more effectively than crystalloids, with the same increase in cardiac output being achieved by smaller volumes and with less haemodilution. The crystalloid proponents argue that the interstitial space is depleted in conditions of hypovolaemia because of fluid shift into intravascular and intracellular compartments.[10]

Table 1 Starling equation

$$J_v = K_{fc}[(P_c - P_i) - \sigma_c(\pi_c - \pi_i)]$$

Where
J_v =rate of fluid movement into/out of capillary
K_{fc} =capillary filtration coefficient
P_c =capillary hydrostatic pressure
P_i =tissue fluid hydrostatic pressure
σ_c =reflection coefficient
π_c =capillary colloid osmotic pressure
π_i =tissue colloid osmotic pressure

The interstitial space fills more readily after crystalloid resuscitation. Because of this, the volume of fluid required is two to three times greater than when using colloids, resulting in an increased risk of tissue oedema. Sponsors of the crystalloid school maintain that this is not harmful despite the fact that tissue oedema has been associated with tissue hypoxia and has been implicated in delayed healing of bowel anastomoses.[11] Despite the increased volumes required, crystalloid resuscitation is cheaper than the colloid equivalent (table 2).

Velanovich analysed the mortality data from a number of clinical trials and concluded that after trauma, or in instances when the capillaries are likely to have increased permeability, resuscitation is best achieved with crystalloids.[12] In other circumstances—such as during major elective surgery—mortality rates may be reduced by using colloids.

The most appropriate resuscitation regimens undoubtedly involve the use of both crystalloids and colloids. Criteria for volume administration include tachycardia, hypotension, low filling pressures, reduced urine output, metabolic acidosis and increasing core-peripheral temperature gradient, although it should be remembered that a child can maintain a normal heart rate and systemic blood pressure despite a 25% loss of circulating volume. Volume administration should not be based on reflex prescribing—'He looks volume depleted, therefore give 10 ml/kg of plasma'. An individual patient's fluid requirements should be based on the aetiology of the volume depletion, and the most appropriate fluids should be used in adequate volumes.

Intravenous fluids available

CRYSTALLOIDS

(1) Dextrose

Because dextrose is rapidly metabolised after intravenous administration, 5% or 10% dextrose solutions act as free water, quickly equilibrating

Table 2 Cost of volume replacement by various agents

Fluid	*Cost in £ per 500 ml*
4·5% Albumin	33·00
20% Albumin (100 ml)	(37·00)
Hespan	16·72
Pentaspan	15·70
Gelofusine	3·56
Haemaccel	3·81
Rheomacrodex	6·51
Macrodex	4·11
Normal saline	0·78
Hartmann's solution	0·88

Table 3 Chemical basis and source of clinically important colloids

	Natural	*Hydroxyethyl starches*	*Gelatins*	*Dextrans*
Chemical basis	Protein	Carbohydrate	Protein	Carbohydrate
Source	Blood	Amylopectin	Bovine collagen	Bacterial synthesis
Examples	Albumin FFP	Hespan Pentastarch Pentafraction	Gelofusine Haemaccel	Dextran 40 Dextran 70
Excretion	Liver/ kidneys	Amylase/RES/ kidneys	Kidneys Proteases	

FFP, fresh frozen plasma, RES, reticuloendothelial system

Table 5 Molecular weight definitions

Weight average molecular weight (M_w)

$$M_w = \frac{\text{sum of each molecule's weight}}{\text{total mixture's weight} \times \text{weight of the molecule}}$$

Number average molecular weight (M_n)

$$M_n = \frac{\text{mass of the sample in grams}}{\text{total number of chains}}$$

After Hulse and Yacobi.[18]

between the intracellular and extracellular fluid compartments For every 100 ml infused, only 7·5 ml will remain in the intravascular space for a useful period of time, so dextrose solutions are inappropriate for intravascular fluid resuscitation.

(2) Isotonic crystalloid solutions

Isotonic crystalloids (for example, normal saline and Hartmann's solution) equilibrate rapidly throughout both the interstitial and intravascular spaces, so approximately one quarter of the administered volume will remain within the intravascular space.

(3) Hypertonic saline solutions

These have shown a resurgence of popularity. Small volumes of 7·5% saline have successfully maintained the circulation after hypovolaemic shock.[13 14] Their role in paediatrics has not yet been assessed, and hypertonic saline may prove inappropriate for neonates with immature sodium handling.[15]

COLLOID SOLUTIONS

Colloid solutions, both natural (for example, human albumin solutions) and the synthetic macromolecules (for example, the gelatins, hydroxyethyl starches, and dextrans), theoretically remain within the intravascular space. Thus, volume for volume, they provide a greater and more sustained haemodynamic response than crystalloids. In the UK, standard paediatric practice is to use natural colloids for resuscitation. Although synthetic colloids are used sporadically, there has been a reluctance to use them routinely because of a lack of clinical trials concerning their use in children.

BASIC STRUCTURE OF COLLOIDS

The chemical basis and source of the clinically important colloids are shown in table 3, and table 4 summarises the pharmacology. The two molecular weights quoted for synthetic colloids are defined in table 5. The weight average molecular weight (M_w) determines the viscosity, while the number average molecular weight (M_n) gives an indication of the osmotic pressure exerted by the fluid. Albumin is monodisperse—that is, all of the molecules within a solution are the same size and both M_w and M_n are 69 000. All of the synthetic colloids are polydisperse, and have different values for M_w and M_n (table 4).

PHARMACOLOGY OF INDIVIDUAL COLLOIDS

Natural colloids

(A) Fresh frozen plasma—fresh frozen plasma is extracted from donated blood and because it is unpasteurised it has the potential to transmit blood borne infections. The Consensus Conference held at the National Institutes of Health has laid down strict guidelines for the administration of fresh frozen plasma, concluding that there is no justification for its use as a volume expander.[19]

(B) Albumin—Human albumin solution is derived from donated blood by fractionation and/or plasmapheresis. It is produced as a 4·5% solution (iso-oncotic with plasma) or as more concentrated (hyperoncotic) 10% or 20% solutions of 'salt poor' albumin.[20]

Albumin persists within the body for about 20 days, although its duration of action within the intravascular compartment varies from less than two hours to more than a day.[21]

Although freely donated, the processing of human albumin is expensive (table 2).

Synthetic colloids

(A) Gelatins—The gelatins tend to be considered as a homogeneous group but, because of different manufacturing processes,[22] the individual solutions have differing properties, particularly in the incidence of adverse reactions. The new

Table 4 Characteristics of various colloids[10 16 17]

	Albumin	*Gelofusine*	*Haemaccel*	*Hetastarch*	*Pentastarch*	*Dextran 40*	*Dextran 70*
M_w (kDa)	69	30	35	450	200	40	70
M_n (kDa)	69	22·5	24·5	71	35	25	39
Sodium (mmol/l)	130–160	154	145	154	154	154	154
Potassium (mmol/l)	1	<0·4	5·1	0	0	0	0
Calcium (mmol/l)	0	<0·4	12·5	0	0	0	0
Duration of action (hours)	6	3–4	3–4	>8	6–8	3–4	6–8
Survival in body (days)	21	7	7	2–65	7	6	28–42
Water binding (ml H_2O/g colloid)	18	42·8	41·7	20	30	37	29

generation gelatins are widely used within Europe. In the UK the two most commonly used solutions are: (1) Gelofusine (B Braun) which is a 'modified fluid' or succinylated gelatin and (2) Haemaccel (Hoechst) which is a polygeline, or urea-linked gelatin.

For intravascular volume expansion, they produce an effect which is almost equivalent to albumin, with a duration of action of three to four hours. In vitro evidence suggests that in conditions associated with capillary leak, Gelofusine may be more efficacious than albumin.[23]

(B) Hydroxyethyl starches (HES)—HES are derived from amylopectin which is stabilised by hydroxyethylation to prevent rapid hydrolysis by amylase. The HES solutions show a discrepancy between M_w and M_n (table 4) because they contain molecules with a wide range of molecular weights, the smallest of which will be rapidly excreted by the kidneys, with the largest being taken up by macrophages of the reticulendothelial system. The greater the degree of substitution by hydroxyethyl groups, the more resistent the molecule is to breakdown by amylase and, therefore, the longer the survival within the body and the circulation.

Of the available HES solutions, the highest degree of substitution (seven hydroxyethyl groups per 10 of glucose) is seen in hetastarch (Hespan, Du Pont). Its intravascular effect may last up to 24 hours and its survival within the body is between two and more than 60 days.[18 24 25]

Pentastarch (Pentaspan, Du Pont) has recently received a product licence in the UK. It has five groups per 10 of glucose. Although it still contains a large range of molecular sizes, it does not include molecules with a weight greater than a million daltons. This gives the compound the advantage of a shorter persistence within the body, but with a similar efficacy to hetastarch.[26 27]

By diafiltering pentastarch, all of the molecules with a M_w of less than 100 000 daltons can be removed. This fluid (Pentafraction) is not commercially available, but preliminary animal work has suggested that its use may be associated with a reduction in capillary leak.[9 28 29]

(C) Dextrans—Because of their high incidence of adverse effects, the dextrans are inappropriate for volume expansion in paediatrics. The two most commonly encountered dextrans are dextran 40 (for example, Rheomacrodex, Pharmacia) and dextran 70 (for example Macrodex, Pharmacia), the number representing the M_w.

ADVERSE EFFECTS OF COLLOIDS

(1) Anaphylactoid reactions

These have been reported with both natural[30] and synthetic[31] colloids. The reactions may be mild/moderate or severe as classified by Ring and Messmer,[32] and the precise causes of the reactions remain unclear. Release of histamine by the gelatins has been suggested: firstly, because the incidence is higher with urea linked rather than succinylated gelatins (0·1% and 0·05% respectively) and the former has been associated with free di-isocyanate, which causes histamine release; and secondly, the incidence of allergic reactions can be reduced by pretreatment with H_1 and H_2 blockers.[33]

The overall incidence of anaphylactoid reactions to HES is quoted at 0·08%, the majority of which are mild, although severe reactions have been reported.[34]

The dextrans elicit the worst reactions, both in incidence and severity. These are mediated by dextran reactive antibodies which trigger the release of vasoactive mediators,[33] and can be reduced by pretreatment with a hapten. The incidence of cardiac arrest associated with the dextrans, together with their adverse effects on haemostasis and interference with the cross matching of blood are the main factors in their unpopularity.

(2) Coagulation effects

Dilutional effects are seen with all the colloids (except fresh frozen plasma) but the polysaccharides have been associated with abnormalities of haemostasis which are more than simply dilutional. In particular, factor VIII concentrations may be appreciably reduced.[35] Although in vitro tests may be altered by HES, the effects are rarely of clinical significance[36–38] unless massive volumes are infused.[39] The coagulation effects of the dextrans are more pronounced, and the dextrans are therefore used to reduce the incidence of postoperative venous thrombosis and fatal pulmonary embolism.[40] As these complications are exceedingly rare in general paediatric surgery, they do not provide an indication for the use of dextrans in infants and children, although dextran 40 is used in the postoperative period after orthotopic liver transplantation in an attempt to reduce thrombotic complications in the anastomosed vessels.[41]

(3) Risks of infection

The albumin solutions used in the UK are prepared from donated blood which is screened for antibodies to certain blood borne diseases. Because recently infected donors may carry a virus against which antibodies may not yet have been raised, the potential for infection (for example, with HIV or the hepatitis viruses) remains should the pasteurisation process fail.

(4) Interference with laboratory investigations

The polysaccharides may interfere with cross matching reactions and estimations of the erythrocyte sedimentation rate by 'coating' the red cells and causing their aggregation. The effects of HES can be reversed by washing the cells with saline. The effects of dextran are long lasting, which is a major disadvantage in patients requiring blood after dextran administration.

The dextrans have caused false positive glucose analysis results,[42] and, together with Haemaccel, may interfere with the biuret determination of serum total protein.[43] The gelatins migrate within the α_2-fraction in electrophoresis, but do not appear to affect immunological assays.[42]

Amylase contributes to the elimination of HES from the body, and the serum amylase value may double after HES infusion.[44]

CLINICAL STUDIES WITH SYNTHETIC COLLOIDS

There is a wealth of literature describing the adult experience with synthetic colloids, and a corresponding paucity of paediatric studies.

Boon has published his experience with Haemaccel over 14 years in more than 8000 patients,[45] whilst Lundsgaard-Hansen and Tschirren[46] have reported 20 years experience with Gelofusine. Both papers conclude that these two fluids are safe, effective, and worthwhile fluids for volume replacement. In critically ill patients, Gelofusine has been associated with increased oxygen consumpton.[47]

Six per cent HES was equal to albumin for peroperative volume replacement during paediatric anaesthesia.[48] HES has been used satisfactorily in the pump prime for bloodless open heart surgery in children who are Jehovah's Witnesses.[49] It has been studied extensively in adults with the conclusion that there is no difference between HES and albumin, with HES offering a considerable cost saving.[36 50–52]

Despite their unacceptable level of adverse effects, there is little doubt that the dextrans are very efficient plasma expanders.[33 53–55]

PRESCRIBING PITFALLS

(1) Serum albumin and measurement of colloid osmotic pressure

Under normal conditions, only half of the body's endogenous albumin is intravascular, but it contributes about 80% of the intravascular colloid osmotic pressure.[56] In critically ill patients, because of the 'acute phase reaction', the serum albumin concentrations may not provide an accurate reflection of the colloid osmotic pressure as the production of acute phase proteins takes precedence over the synthesis of albumin.[57] Albumin may be administered not because volume replacement is required, but because the serum albumin concentration is low.

(2) Inadequate resuscitation

Problems with crystalloid resuscitation are often related to inadequate volumes being administered, because the prescriber fails to allow for fluid movement into the interstitial compartment.

(3) Volume overload

While the gelatins are plasma substitutes, and can be used interchangeably with albumin, the dextrans and hydroxyethyl starches are true plasma expanders—that is, they produce an increase in plasma volume greater than the volume of colloid infused. Although this may be of clinical benefit, the risk of fluid overload and significant haemodilution is greater when administered by unwary prescribers.

Conclusions

Although there are certain indications for natural colloids—for example, after certain open heart operations when massive colloid infusion may be required, synthetic colloids could often be given in their place. Because of their safety, the gelatins (particularly the modified fluid gelatins) are the most appropriate choice but there are situations when the superior plasma expansion of hydroxyethyl starches may be required. Although studies with synthetic colloids in adult patients may be extrapolated to the paediatric population, there remains a need for an evaluation of synthetic colloids in paediatric practice.

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Archives of Disease in Childhood 1992, 67: 654–656

CURRENT TOPIC

The autonomic nervous system—a role in sudden infant death syndrome

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Accepted 22 November 1991

The sudden infant death syndrome (SIDS) is the major cause of infant mortality in developed countries and remains unexplained.[1, 2] While much research related to SIDS over the past 20 years has been into respiratory control, the sleep apnoea hypothesis, this has failed to identify a causal link between poor respiratory control and SIDS.[3, 4] The autonomic nervous system is the overall controlling system regulating many of the rescue responses necessary to preserve integrity in a variety of potentially life threatening situations. Given the importance of a functioning autonomic nervous system for survival, and the 'inappropriateness' of most SIDS deaths[1, 2] there has been little systematic study of how best to assess autonomic function in infants.

Adelson in 1961 postulated a lethal vagocardiac reflex as a cause of death in SIDS[5] and Fraser and Frogatt suggested a cardiac arrythmia associated with a prolonged Q-T interval.[6] However, a large prospective study failed to show any difference in Q-T interval length between infants with SIDS and controls.[7] Salk *et al* proposed a link between autonomic dysfunction and SIDS[8] as did Schwartz *et al* who suggested that abnormal development of the sympathetic innervation of the heart might lead to ventricular fibrillation and death.[9, 10] Southall in a large prospective study found infants who had a future sudden infant death to have more sinus tachycardia and a higher heart rate than controls.[11] Kelly *et al* found these infants to have a higher mean heart rate and more frequent episodes of bradycardia than controls.[4] Additional autonomic effects include profuse watery salivary gland secretions and increased sweat production—both reported associations with SIDS.[1, 2, 12, 13] A group of infants who had sustained an acute life threatening episode (ALTE) have been reported to have exaggerated oculocardiac induced (vagally mediated) cardiac asystoles.[14]

SIDS infants have also been shown to have a lower number of small myelinated vagal nerve fibres, suggesting abnormal or delayed development,[15] in addition to gliosis in the brain stem area controlling vagal function.[16] Carotid bodies from SIDS infants have been shown to contain increased concentrations of dopamine and noradrenaline[17] further suggesting an abnormality in the cathecolaminergic autonomic system. The finding that 84% (21 of 25) of SIDS infants had a significant increase in pulmonary neuroendocrine cell numbers compared with control infants may imply a failure of autonomically mediated discharge of intracellular granules[18] (neuroendocrine cell abnormalities are frequently seen in adults with autonomic neuropathy). Studies examining the intrinsic cardiac conduction system have produced conflicting results perhaps reflecting the difficulty in obtaining suitable control specimens for SIDS infants inherent in any postmortem study.[19, 20]

Many SIDS infants are said to have a mild respiratory tract infection,[1, 21] diagnosed by a history of snuffles or of being 'chesty' in association with the presence of lung inflammatory cell infiltrates at necropsy, and the roles of nasal obstruction and respiratory infection in SIDS have been debated for years. Most SIDS infants have no other evidence of an acute infection and nasal mucosal thickness and mucus production are under autonomic control. Recently 22 of 50 infants with snuffles, compared with four of 50 control infants, were shown to have postural hypotension raising the possibility that in some infants snuffles may be due to a disturbance in vasomotor tone rather than infection.[22] The intra-alveolar and peribronchiolar inflammatory cell infiltrates found in SIDS[23] are the probable local source of the increased IgA and IgM antibody concentrations reported in lung lavage fluid in SIDS infants.[24] Barrett (in 1954) speculated that these cells might represent a continued 'mild irritation' rather than an acute infection or inflammation and did not feel that they represented an adequate cause of death.[23] Local airway irritant responses are neuropeptide mediated (neurogenic inflammation) by the autonomic nervous system,[25, 26] causing enhanced vascular permeability and inflammatory cell (mononuclear, lymphocytic, and polymorphonuclear) chemotaxis. Substance P is the most abundant lung mucosal neuropeptide identified to date and has been shown to stimulate activated human lymphocytic production of IgA and IgM.[27, 28] It is known that laryngeal and upper airway 'irritant' receptors can trigger neurogenic inflammation in the upper and lower respiratory tract.[29]

While the role of gastro-oesophageal reflux in SIDS is still debated there is no doubt that reflux of even small quantities of acid gastric contents could stimulate laryngeal and upper airway irritant receptors[30] as could parental smoking—a risk factor for SIDS.[31] Consequently it is possible that the neuropeptide mediated irritant response may, once triggered, be exacerbated or continued by concomitant autonomic dysfunction. The abnormal vagal nerve fibres described in SIDS infants are most probably those involved in these responses.[15]

Investigation of autonomic function

Given the likely importance of a normally functioning autonomic nervous system in any 'stressful' situation, including illness, there is relatively little published work relating to autonomic function testing in children. Investigation of autonomic function in children was originally confined to the oculocardiac reflex and the heart rate response to an abdominal air stream stimulus.[32] More recently there has been measurement of heart rate variability, although most studies failed to take account of known confounding factors such as sleep state, percentage of awake time during the recording, the effects of a recent feed, and the ambient temperature.[4 33–35] Investigation of blood pressure responses was limited because of cuff size and difficulties with technique until the development of blood pressure measurement by Doppler and oscillometric methods.

In adults autonomic function testing is largely confined to cardiovascular responses (heart rate and blood pressure) to a wide variety of manoeuvres some of which are detailed below. Any abnormalities detected are thought to reflect widespread autonomic dysfunction including the non-cardiovascular autonomic nervous system.[36–38] Parasympathetic function is investigated by means of the heart rate beat to beat variability and the heart rate response to the Valsalva manoeuvre, deep breathing (expiration:inspiration ratio), and to standing, which is measured as the ratio of the longest R-R interval (called R-R max and generally the 30th beat after standing in adults) to the shortest R-R interval (R-R min or the 15th beat after standing in adults) and called either the 30:15 or the R-R max:min ratio. Sympathetic function is assessed by the blood pressure response to sustained hand grip and the blood pressure response to a change from the supine to the upright position. In adults autonomic dysfunction is graded in degrees of severity and there is an association between increasing dysfunction and sudden, unexpected and unexplained death.[37 38]

Using the heart rate long term beat to beat variability in quiet sleep and the heart rate and blood pressure responses to postural change we have recently shown that autonomic dysfunction is an uncommon occurrence (0–6%) in a group of healthy 11 week old infants.[39] Using the same technique autonomic dysfunction was present in 12·5% of infants where a sibling had died from a SIDS and 46% of infants suffering a well defined severe ALTE. By decreasing the ambient air temperature from 25°C to 20°C the percentage of the near miss group in this study shown to have autonomic dysfunction rose from 46% to 77%. In addition one infant in the near miss group died 14 hours after autonomic function testing showed him to have autonomic dysfunction as shown by a decreased heart rate variability (mean (SD) long term variability 10·3 (6·5), 21 control infants mean (SD) 21·5 (3·3) beats/minute) and a posturally induced fall of 14% in resting blood pressure associated with a progressive bradycardia. A detailed postmortem examination failed to demonstrate a cause of death and showed an increased number of pulmonary neuroendocrine cells and gliosis in the area of the brain stem controlling autonomic/vagal function (postmortem results courtesy of Dr J Gillan).[16]

Recent work in adults has re-emphasised the importance of the autonomic nervous system in the genesis of malignant ventricular arrythmias.[40] As the majority of sudden cardiac deaths in adults occur in people with coronary artery disease most of the published work relates to acute myocardial ischaemia and the period after infarction and sudden death.[41] In this group poor autonomic function, as demonstrated by a reduced heart rate variability, has been shown to be a very powerful predictor of life threatening arrythmic events and sudden, frequently unpredicted, deaths. A recent *Lancet* editorial comments that 'the evidence linking post infarction autonomic dysfunction to arrythmic propensity is now overwhelming'.[42] In adults the combination of hypoxia, secondary to coronary artery disease, and autonomic dysfunction is felt to be the setting in which both combine to produce a lethal arrythmia. Infants with autonomic dysfunction may similarily be arrythmogenic and at increased risk of cardiac arrythmias perhaps requiring an additional stimulus such as hypoxia for their occurrence. The most likely causes of hypoxia in well infants would include sleep apnoea, loss of upper airway control, and ventilation-perfusion mismatching in the lungs. Sleep apnoea has been extensively studied as previously mentioned, although the effect of excess bedding and fever on respiratory and autonomic function need further study.

Upper airway resistance during expiration, by providing an expiratory brake, generates a positive airway pressure and is important in maintaining an adequate functioning lung volume.[43–45] Lung volume in adults has been shown to increase with increasing oronasal airway resistance associated with partial nasal occlusion and to decrease with the drop in resistance associated with mouth breathing that occurs with total nasal obstruction.[43] The nasal airway provides up to 50% of upper airway resistance in infants.[46] In lambs the loss of the normal expiratory airway pressure caused irregular breathing, hypoxia, and hypercapnia especially when the metabolic demand was low.[47] The active expiratory response, described by Hering and Breuer, is directly related to the magnitude of lung inflation when the vagi are intact.[48] Infants, with a pliable chest and decreased muscle tone especially in rapid eye movement sleep, could most economically maintain lung volume by controlling expiratory resistance and duration.[49]

An upper airway resistance that is too low could interfere with lung volume maintenance which is integral to many aspects of lung function. Excessive upper airway resistance would increase the required inspiratory pressure with the consequent risk of pharyngeal closure during inspiration and consequent hypoxia.[1 50 5]

The autonomic system controls ventilation-perfusion matching in the lungs via both central and local reflex mechanisms that are interdependant The local control of ventilation-perfusion matching is thought to involve the pulmonary neuroendocrine cell system—shown to be frequently abnormal in SIDS.[18] Severe arterial hypoxaemia secondary to intrapulmonary shunting and ventilation-perfusion mismatching has already been proposed as the cause of sudden unexpected death in a group of infants presenting with cyanotic episodes.[52] Infants suffering an acute life threatening episode have been shown frequently to have autonomic dysfunction,[39] and the occurrence of hypoxia would increase any arrythmogenic potential in this group.

Infants with autonomic dysfunction may be at risk from sudden unexpected deaths by simply not being as well equipped to deal with a variety of life threatening situations and succumb where infants with an optimally functioning autonomic nervous system would survive—for example, by failure of the hypoxic arousal response. Alternatively infants with autonomic dysfunction may, like adults, be more arrythmogenic and any additional factor which further increases this tendency, such as hypoxia, could result in a lethal arrythmia. At present there is an urgent need to establish the best method for assessing autonomic function in infants and its subsequent role, if any, in SIDS.

I wish to acknowledge the generous financial support of the Friends of the Rotunda and the Irish Sudden Infant Death Association and to thank Audrey Dixon for typing the manuscript.

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Archives of Disease in Childhood 1992; 67: 657–661

REGULAR REVIEW

Biological role of lactoferrin

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Lactoferrin is an iron-binding protein closely related in structure to the serum iron transport protein transferrin. Unlike transferrin, only traces are normally present in serum, and it is instead found mainly in milk and other external secretions, and in the secondary granules of neutrophils. Although lactoferrin was first isolated 30 years ago, its biological role remains unclear. Some aspects of its function were discussed about 12 years ago in this journal,[1] and this review will attempt to reassess the function of lactoferrin in the light of the large amount of new information that has accrued since then.

Knowledge of the structure of lactoferrin has been advanced by recent *x* ray crystallographic studies, and the structure and iron binding properties of lactoferrin are reviewed in detail elsewhere.[2 3] Briefly lactoferrin, like transferrin, reversibly binds two ferric ions, for which synergistic binding of an anion, usually bicarbonate or carbonate, is necessary. However, its affinity constant for iron is 300 times greater than that of transferrin, and even in the presence of a competing iron chelator such as citrate it can retain iron down to pH 3 or less while transferrin loses it at pH 5. Unlike transferrin, lactoferrin is strongly basic. Human lactoferrin has been cloned and sequenced[4] and the recombinant protein expressed in baby hamster kidney cells.[5]

Lactoferrin in milk

Human milk is particularly rich in lactoferrin, the concentration ranging from about 7 g/l in colostrum to about 1 g/l in mature milk, though it may rise again towards the end of lactation.[6 7] A similar pattern is seen in the cow, but importantly the concentration in mid-lactation milk is very much lower, only about 0·1 g/l.[8] Lactoferrin concentrations were normal in iron deficient mothers,[9] but lower in mothers who were generally malnourished,[10] which suggests that protein energy malnutrition rather than iron influences lactoferrin synthesis in the mammary gland. Although lactoferrin is found in the milk of some other species, it is completely absent in others, such as the rat, rabbit, and dog.[6] The milk of the rat and rabbit do however contain significant amounts of transferrin, but the milk of the dog contains neither protein, even though the iron content is exceptionally high.[6] The fact that lactoferrin is absent from the milk of some species is a point worth bearing in mind when considering its possible biological function.

Human milk contains 3·6–12·5 μmol/l of iron, and of this only 60–70% is in the whey fraction, the remainder being in the lipid fraction (11–20%) or bound to casein (2–14%).[11] As a consequence, milk lactoferrin is only 6–8% saturated with iron, presumably because of the difficulty in gaining access to iron in the lipid fraction or casein micelles.

Association of lactoferrin with other molecules

Lactoferrin is very prone to binding to other macromolecules. These include other milk proteins such as IgA, casein, secretory component, albumin, lysozyme, and β-lactoglobulin.[12] Lactoferrin also binds to DNA.[13] A report of multiple forms of lactoferrin in human milk, some of which exhibit ribonuclease activity,[14] may arise from an interaction between lactoferrin and milk ribonuclease. Bovine milk ribonuclease is, like lysozyme, a small basic protein (molecular weight 13 600),[15] and some ribonuclease activity in human milk was also associated with a molecule of this size.[14] So far no clear biological role has been established for this propensity of lactoferrin to interact with other proteins.

Biological functions of lactoferrin

BACTERIOSTATIC ACTIVITY

Almost all bacteria require iron for growth, and because of their iron sequestering properties, the iron free (apo) forms of lactoferrin and transferrin are able to impede iron utilisation by bacteria. A large number of studies, reviewed elsewhere,[16] have demonstrated a bacteriostatic effect and in some cases a bactericidal effect of lactoferrin in vitro on a wide range of microorganisms, including Gram positive and Gram negative bacteria, aerobes, anaerobes, and yeasts. However, mechanisms other than simple iron withholding may be involved in the antibacterial action of lactoferrin, such as blockade of microbial carbohydrate metabolism[17] or destabilisation of the bacterial cell wall, perhaps through binding of calcium and magnesium.[18] Lactoferrin may synergise with other antibacterial proteins such as lysozyme, which is also present in milk. In this case even the iron saturated form is active, and inhibition results from agglutination by lactoferrin of bacteria whose cell wall has been modified by lysozyme.[19] Antibodies can also enhance the bacteriostatic action of lactoferrin,[20] probably by blocking production or uptake of microbial siderophores.

Lactoferrin may also possess antiviral activity, as it could protect mice against polycythaemia due to Friend virus.[21] This appears to be an indirect effect, perhaps via a reduction in target cell proliferation, and is probably related to the proposed inhibitory role of lactoferrin in myelopoiesis (see below).

In vivo, lactoferrin in milk might exercise its inhibitory effect on microbial growth in the mammary gland, in the intestine of the newborn, or both. Its role as a defence against infection in the human mammary gland appears not to have been investigated, but in cattle concentrations of lactoferrin increase during intramammary infection,[22] suggesting a possible role as a mammary non-specific defence mechanism. Conditions in the bovine mammary gland immediately before parturition and during involution favour antimicrobial activity of lactoferrin as concentrations of bicarbonate are higher and those of citrate lower than in milk.[22 23] Thus lactoferrin might perform a role in preventing infection of the mammary gland, particularly at parturition and involution.

It has frequently been suggested that the antimicrobial activity of lactoferrin plays a part in the selection of the intestinal flora of the newborn and preventing colonisation by enteropathogenic organisms. The conditions in the intestine of the newborn may be more favourable for lactoferrin than those in the lactating mammary gland, as citrate is rapidly absorbed and intestinal fluid has a high concentration of bicarbonate, although this function might be adversely affected by the proteolytic enzymes present in the intestine, as discussed below. Nevertheless, despite the wealth of in vitro data, attempts to establish an in vivo antimicrobial role for lactoferrin have generally yielded disappointing results. The much quoted experimental study of Bullen *et al*,[20] which suggested a protective effect of lactoferrin in newborn guinea pigs infected with *Escherichia coli* is open to other interpretations, as discussed previously in this journal.[1] However, addition of chicken ovotransferrin to cows' milk was able to reduce mortality and bacterial counts in young guinea pigs infected with enteropathogenic *E coli*.[24] Two more recent clinical studies have analysed the faecal flora of infants fed bovine lactoferrin (in one case in conjunction with bovine IgG) and failed to find any significant difference between infants fed lactoferrin-supplemented formula and controls fed unsupplemented formula.[25 26] However, differences between bovine and human lactoferrins (such as resistance to proteolysis, discussed below) may mean that bovine lactoferrin is not an appropriate substitute for the human protein, and recombinant DNA technology now offers the possibility of obtaining sufficient human lactoferrin for clinical trials.

Thus although it is now well established that breast feeding offers protection to the newborn infant against gastrointestinal infection, the part played by lactoferrin must still be considered unproved until the wealth of in vitro data showing antimicrobial activity is supported by convincing in vivo data, particularly from clinical trials. The possibility that lactoferrin might exert a systemic protective effect also deserves further investigation, as studies in mice have shown that lactoferrin has a protective effect in experimental *E coli* septicaemia that is independent of its iron content.[27]

ROLE OF LACTOFERRIN IN INFLAMMATION AND THE IMMUNE SYSTEM

A number of studies suggest that lactoferrin may mediate some of the effects of inflammation and have a role in regulating various components of the immune system. It was proposed some years ago that lactoferrin released by degranulating neutrophils mediated the hyposideraemia of inflammation by removing iron from plasma transferrin and short circuiting it to macrophages of the reticuloendothelial system, where it was incorporated into ferritin.[28] However, iron uptake by macrophages from lactoferrin is at best extremely slow,[29] and there is no recycling of the protein as occurs with transferrin, as lactoferrin that has bound to monocytes cannot subsequently rebind to these cells.[30] In addition, the rate of exchange of iron between transferrin and lactoferrin at physiological pH is likely to be extremely slow, and finally neutrophil-derived lactoferrin differs from milk lactoferrin, which was used in most studies, in lacking the terminal fucose residues in its glycan chains that are required for binding to macrophages.[31] It has also been found in mice that interleukin-1 induces hypoferraemia even in the presence of neutropenia,[32] suggesting that lactoferrin is unimportant. Thus it now seems unlikely that lactoferrin plays a significant part in the hypoferraemia of inflammation.

Lactoferrin might also contribute to the bactericidal activity of neutrophils by two opposing mechanisms. In the apo form it may perform an iron withholding function and prevent growth of phagocytosed bacteria.[33] On the other hand iron-lactoferrin may provide iron that can catalyse the production of free radicals which lead to microbial killing within the phagolysosome of phagocytic cells.[34] The ability of lactoferrin to promote formation of free radicals is probably confined to acidic conditions such as those within the phagolysosome, as at physiological pH it is more likely that lactoferrin inhibits radical production by scavenging catalytic 'free' iron.[35] A role for lactoferrin in the antimicrobial activity of neutrophils is supported by the finding that patients whose neutrophils lack specific granules suffer from recurrent infections.[36]

Lactoferrin may also act as an inhibitor of secretion of granulocyte-monocyte-colony stimulating factor (GM-CSF).[37] This complex area has been intensively investigated and is reviewed fully elsewhere.[38] In summary, lactoferrin appears to act by decreasing synthesis of interleukin-1 which is necessary for GM-CSF production. Iron-lactoferrin was more effective than apo lactoferrin but it is not known what if any part is played by iron. Lactoferrin isolated from neutrophils lacking receptors for the Fc region of immunoglobulin or from neutrophils of leukaemia patients was inactive, though the reason for this is unclear as possible differences between the active and inactive forms of lactoferrin were not investigated.

The role of lactoferrin as an inhibitor of myelopoiesis is somewhat controversial, however, as some reports have failed to find any inhibitory effect.[39 40] Some aspects of the original studies such as the extremely low concentrations of lactoferrin required for activity (10^{-17} M) and a discrepancy between the isoelectric point of the active component (6·5)[37] and purified lactoferrin (8·7)[41] require explanation. Further work is needed, particularly with a view to establishing how lactoferrin itself initiates these events at the molecular level, before its role in myelopoiesis can be regarded as fully established.

Lactoferrin has been reported to affect various aspects of the immune system, such as inhibiting in vitro antibody synthesis,[42] regulating monocyte/macrophage cytotoxic activity,[43 44] and affecting lymphocyte proliferation.[45–48] In most of these studies the mechanism by which lactoferrin carries out these functions was not established. The effect on lymphocyte proliferation is unclear, as some authors have reported enhancement[45] and others inhibition.[46 47] Possibly this may depend upon culture conditions, as recent work has suggested that apolactoferrin can overcome the inhibitory effect of 'free' iron on lymphocyte proliferation, but itself inhibits proliferation when iron is bound to transferrin.[48] Activation of T lymphocytes induces the presence of lactoferrin-binding molecules in the cell membrane,[45 49] and binding to B cells has also been reported.[50] However, further work is required before an immunoregulatory role for lactoferrin can be clearly established.

ROLE OF LACTOFERRIN IN THE ABSORPTION OF IRON

The greater bioavailability of iron and higher concentration of lactoferrin in human milk compared with cows' milk suggests that lactoferrin might promote iron absorption in breast fed infants. In a previous review in this journal it was suggested that lactoferrin actually had an opposite effect, and served as an additional control of iron absorption during the neonatal period.[1] More recent clinical trials have failed to demonstrate any improvement in iron absorption in infants fed formula milk supplemented with (bovine) lactoferrin.[51 52] A study in rats did show that feeding lactoferrin improved iron status[53] but the rat is a poor model for such studies as the milk of this species does not contain lactoferrin. Studies in piglets,[54] weanling mice,[55] or infant rhesus monkeys[56] showed that the bioavailability of iron bound to lactoferrin was no better than that of inorganic iron.

If lactoferrin were to have a role in iron absorption one might expect a receptor to exist in mucosal cells. Lactoferrin-binding proteins have been identified in the microvillus membranes of rabbit,[57] mouse,[58] and rhesus monkey enterocytes.[59] The molecular weights and binding characteristics of these proteins differ between species. However, there is so far no evidence that these membrane proteins actually mediate uptake or transport of lactoferrin-bound iron in mucosal cells. Given that there are also studies suggesting that lactoferrin may inhibit iron absorption, reviewed previously,[1] our earlier conclusion that lactoferrin controls rather than promotes iron absorption in the neonate still seems to be valid.

PROTEOLYTIC DEGRADATION OF LACTOFERRIN AND SURVIVAL IN THE GASTROINTESTINAL TRACT

A role for lactoferrin in iron absorption or establishment of the microbial flora of the gut presupposes a certain resistance to the conditions within the gastrointestinal tract. In vitro studies have found that apolactoferrin is more sensitive to the action of trypsin than iron-lactoferrin, although human apolactoferrin was less sensitive than bovine.[60] Lactoferrin is also degraded by gastric fluid from premature babies, though unlike transferrin or casein more degradation occurred at pH 3·2 than at pH 1·8.[61] However the gastric pH will be raised by the buffering capacity of milk proteins, and the intestinal flora and the velocity of transit also affect digestion of lactoferrin.[9] Studies of lactoferrin isolated from the faeces of newborn infants fed cows' milk supplemented with human lactoferrin or bovine lactoferrin showed that iron-lactoferrins survived better than the apo forms and, surprisingly, bovine lactoferrin was more resistant than human.[62] Partly digested proteins maintained their capacity to bind iron after excretion, and fragments of human lactoferrin obtained by acid hydrolysis were still able to bind to the putative rhesus monkey mucosal receptor, albeit with lower affinity than intact lactoferrin.[63]

Intact lactoferrin and fragments have been detected in the urine of premature infants receiving human milk,[64] arising apparently from lactoferrin absorbed across the gut.[13] This suggests that lactoferrin is partially degraded in the gut and that significant absorption of this protein occurs in the premature infant. However, some fragments may be present before ingestion, as in contrast to a previous report[65] we have recently found lactoferrin fragments in human and bovine milk.[66] It seems less likely that lactoferrin absorption occurs in term infants, as no difference in plasma lactoferrin concentrations was found between breast and bottle fed infants.[67]

ACTIVITY OF LACTOFERRIN AS A GROWTH FACTOR

Recent studies have suggested that lactoferrin may promote cell growth. As well as possibly promoting lymphocyte proliferation (see above), human lactoferrin also stimulated growth of various cell lines.[29 68] It also enhanced proliferation of rat mucosal crypt cells,[69] which suggests that it might play a part in maturation of the intestine in the newborn. The possibility that lactoferrin acts as a growth factor is supported by the presence of high concentrations of lactoferrin in some tumours,[70] although the reasons for these high concentrations are unclear. In some cases growth promotion required iron[68] whereas in others iron was unimportant.[29 69] The mechanism by which lactoferrin is able to stimulate cell growth is therefore unclear, but seems unlikely to involve iron transport in an analogous manner to transferrin, as lactoferrin is not internalised and little or no iron is taken up from lactoferrin.[29] It might involve activation of membrane oxidoreductase activity.[71]

Conclusion: the biological function of lactoferrin—a unifying hypothesis

Over the past 10 years there has been considerable research on the function of lactoferrin, much of it in areas unrelated to the traditional fields of iron absorption and antimicrobial activity. Despite this, no clear biological role for lactoferrin has been established. Its antimicrobial activity, so well documented in vitro, still awaits convincing in vivo evidence. New studies of iron absorption have generally failed to show that iron in lactoferrin has a higher bioavailability than iron salts, and there is still no direct evidence that lactoferrin actually mediates uptake across the mucosa. Although lactoferrin-binding proteins have been identified in mucosal membranes, these could just as easily serve to regulate iron transport as enhance it. A role in hypoferraemia now seems unlikely, and effects on myelopoiesis and the immune system are either controversial or essentially phenomenological, with little information on how lactoferrin actually mediates these effects. Although lactoferrin receptors or binding proteins have been reported from a wide variety of cells and tissues the molecular structure and binding characteristics of these putative receptors varies considerably, and in many cases binding is relatively non-specific. It may well be that the various apparently unrelated effects of lactoferrin on the immune system arise from its ability to bind to macrophages and lymphocytes. This could alter the surface charge of the cell membrane, with consequent effects on the various cell-cell interactions that have a crucial role in many immunological mechanisms.

We believe that current evidence suggests that lactoferrin, despite its structural similarity to transferrin, does not act as an iron transport protein. Instead, we propose that its role is that of a specialised iron-scavenging protein, designed to act particularly under conditions where transferrin would be less effective at binding iron due to reduced pH, such as exist in the gastrointestinal tract or inflammatory lesions. By binding iron under these conditions it would render harmless 'free' iron that might otherwise cause free radical-mediated damage to sensitive tissues, reduce absorption of unwanted iron in the immediate postnatal period, and decrease its availability to micro-organisms. The ability of lactoferrin to bind to a wide variety of cells and tissues, perhaps without the need for expression of a truly specific receptor, would enhance its ability to prevent free radical-mediated damage or microbial invasion. It would also help to ensure its eventual removal and catabolism via the reticuloendothelial system or by biliary excretion. Further studies, particularly of lactoferrin-cell interactions, may help to establish the validity of this proposal.

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LETTERS TO THE EDITOR

Does growth hormone treatment improve final height attainment of children with intrauterine growth retardation?

SIR,—The potential indications for the therapeutic use of growth hormone have widened with the availability of more abundant supplies of growth hormone. For some of the new potential indications such as Turner's syndrome, intrauterine growth retardation (IUGR), etc, the growth-promoting benefits of growth hormone have usually been assessed in the short term by comparing the changes in height velocity SD score during the first treatment year and the pretreatment year, and, in some instances, by quantitating the psychological benefit gained by improved growth during the middle childhood years. In the long term the benefits of growth hormone can be assessed by comparing final height in a treated group with either that achieved in an untreated group or with the original pretreatment height prediction of the treated group.

In their recent article on the use of growth hormone in children with IUGR, Stanhope *et al* present three year growth data and suggest that the results are rather disappointing.[1] This conclusion is based on the fact that the height for bone age score did not change significantly over the three years of the study With knowledge of the natural history of IUGR, Stanhope *et al* do, however, still believe that their growth hormone treated children may attain a greater final height than would have been the case if they had remained untreated In their discussion Stanhope *et al* state that 'only the continuation of clinical trials such as this until final height will answer the question'. Others might feel that the current results are sufficiently disappointing for the study to be concluded now.

Certainly if the design of the study remains in its present form then, as the authors acknowledge, there is a real possibility that growth hormone treatment will reduce the duration of puberty and compromise final height prognosis. Thus, I would suggest that, if the study is to continue, one of their groups of IUGR children, who received growth hormone during prepubertal life, should not receive growth hormone during puberty. Furthermore, their results emphasise that individual children with IUGR seen by paediatricians around the UK should not be offered growth hormone on an *ad hoc* basis.

Finally, if the authors believe that possible growth hormone treatment induced gain in height for IUGR children can only be interpreted when the children attain final height, is much learnt by publishing the three year growth data?

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1 Stanhope R, Preece MA Hamill G Does growth hormone treatment improve final height attainment of children with intrauterine growth retardation? *Arch Dis Child* 1991,66:1180–3.

Dr Stanhope and Professor Preece comment:
We agree with Dr Shalet that there are many subgroups of children with short stature who may benefit from growth hormone treatment. However the only proved indication to final height is growth hormone deficiency.[1] The reason why we published our three year data of growth hormone treatment in children with intrauterine growth retardation (IUGR) was to emphasise that at the present time such treatment should remain part of a clinical trial and not be offered on an *ad hoc* basis. Height prediction depends on epiphyseal maturation, which is relatively inaccurate over short periods of time, especially in dysmorphic syndromes. However, we believe the natural history of the growth of children with IUGR is sufficiently disappointing to allow our trial to continue [2]

Our study has been modified after one year,[3] when the results from the lower dose growth hormone regimen were disappointing in terms of short term growth rate, and we may modify our trial again Although growth hormone treatment may increase the rate of pubertal progress in a dose dependent fashion, this phenomenon has only been described in children with isolated growth hormone deficiency.[4] Although growth hormone insufficiency is common among children with IUGR,[5] our patients were carefully screened to avoid this ambiguity

We believe that the continuation of this trial is justifiable and having done so, it is our duty to report the findings.

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Kawasaki disease

SIR,—I read with interest the annotation on Kawasaki disease by Levin *et al*.[1] I would like to draw attention to the fact that this disease, like any other vasculitis, can have a predominantly neurological presentation, with an encephalopathic/encephalitic illness I have seen three such patients who all presented with high fever, diminished consciousness, a minimal increase in lymphocytes in the cerebrospinal fluid with normal protein and glucose, and a rash. In one child, a 7 year old, the most striking physical sign was bilateral papilloedema.

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1 Levin M, Tizard EJ, Dillon MJ Kawasaki disease: recent advances. *Arch Dis Child* 1991, 66:1369–72

Late intravenous gammaglobulin treatment in Kawasaki syndrome

SIR,—We wish to comment on the interesting article on intravenous gammaglobulin treatment for Kawasaki disease in which the Archivist mentioned it seems reasonable to treat if the disease is still active.[1] Indeed, the results published by Marasini *et al* suggest a favourable effect of gammaglobulins on established coronary abnormalities, at least in the midterm follow up.[2]

They studied two groups of children with a similar image of coronary abnormalities The first group (nine children) was treated with aspirin (100 mg/kg/day) until the fever disappeared, followed by aspirin (5 mg/kg/day) and dipyridamole (5 mg/kg/day). The second group (seven children) received intravenous gammaglobulins (400 mg/kg/day) for five days after the 10th day from the onset of the disease, when coronary artery abnormalities had already developed

In the first group four patients had a complete resolution of their abnormalities. Five had persistent abnormalities including three with myocardial infarction (one died from his myocardial infarction) In the second group, all coronary abnormalities had resolved during follow up.

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2 Marasini M, Pongiglione G, Gazzolo D, Campelli A, Ribaldone D, Caponnetto S Late IV gammaglobulin treatment in infants and children with Kawasaki disease and coronary artery abnormalities *Am J Cardiol* 1991,68: 796–7.

Inherited metabolic diseases in the sudden infant death syndrome

SIR,—Holton and his coworkers set out to investigate among other causes the prevalence of medium chain acyl CoA dehydrogenase deficiency (MCAD) in cases of sudden infant death syndrome (SIDS).[1] They assert that the claim 'MCAD deficiency could cause 3% of cases of SIDS' is not supported by their findings.

Unfortunately their work, while exhaustive in its scope, demonstrates the difficulty in looking for rare events in small samples. Using binomial probability theorem

$$P(r) = \frac{n!}{r!(n-r)!} p^r q^{(n-r)}$$

the chance of finding 0 cases in a sample of 70 with a true population prevalence of 3% is 0·118. What the authors can say from their work is that with a 0·05 confidence, the true prevalence of MCAD in cases of SIDS is less than 4·2% and using a 0·01 confidence they can state the prevalence is less than 6·4%

Support for their claim of a low prevalence rate of MCAD in SIDS is found in a recent report of carrier rate of the K 329E mutation for MCAD in population screening.[2 3] These estimate the carrier rate to be between 1/40 and 1/107 It is regrettable that the authors' considerable effort in searching for metabolic cause of SIDS was let down by some basic mathematics.

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1 Holton JB, Allen JT, Green CA, Partington S, Gilbert RE, Berry PJ. Inherited metabolic diseases in the sudden infant death syndrome. *Arch Dis Child* 1991;66:1315–7
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3 Matsubara Y, Narisawa K, Tada K, *et al.* Prevalence of K329E mutation in medium-chain acyl-CoA dehydrogenase gene determined from Guthrie cards. *Lancet* 1991,338:552–3

Dr Holton and colleagues comment

Dr Smith is quite correct in pointing out that our negative results in testing for MCAD deficiency in cultured skin fibroblasts from 70 cases of SIDS were not incompatible with claims of a true prevalence of 3%. However, our paper made it clear that our claims that the incidence was less than 3% were based on our findings and those of others, the report of the Lyon group being cited in particular.[1] In an almost identical study to our own, the French workers found no positive findings in 107 SIDS cases. If our results are combined, the binomial probability theorem indicates that the incidence of MCAD is less than 1·7% with 95% confidence, or 2·6% with 99% confidence. On this basis, our claim was not unreasonable.

Perhaps it would be useful to summarise further work relating to the prevalence of MCAD deficiency in SIDS. Two other studies similar to those referred to above have been completed. In Sheffield, 160 SIDS cases (E Worthy, personal communication) and in Edinburgh 120 cases (G T N Besley, personal communication) were tested for MCAD deficiency, all with negative results. If all our results are pooled (457 cases) the prevalence of MCAD deficiency is calculated to be less than 0·65 or 1 00%, with 95 or 99% confidence respectively

Dr Smith concludes that recent reports of population screening for the common MCAD deficiency mutation found carrier frequencies which supported our claim. In addition, the K329E mutation has been sought in DNA extracted from the liver of more than a 100 SIDS cases without finding any homozygotes for the defect [2] Although it is important to appreciate that MCAD deficiency is a cause of sudden, unexplained death, the presentation is not typical of SIDS and it is a rare occurrence.

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Reducing the risk of cot death

Sɪʀ,—The nationwide campaign urging mothers to lay their babies on their backs to sleep is open to question. It would be unfortunate if the leaflets from the Foundation for the Study of Infant Deaths (FSID)[1] and its counterpart from the Department of Health with the unambiguous slogan 'Back To Sleep'[2] are taken to represent the views of paediatricians generally.

The assertion that 'there is no evidence that babies are likely to choke when lying on their backs' belies the considerable research into gastro-oesophageal reflux and laryngeal spasm, which is one of the major aetiological hypotheses Altogether 70% of normal babies have been shown to have reflux during active sleep with 24 hour pH probes.[3] A high incidence of reflux has also been demonstrated in 'near miss' cases using barium swallows, pH probes, and isotope milk scans.[4 5]

Because the prone position is unsafe it does not follow that the supine position is safe. This latest U turn merely replaces one bad position with another. All horizontal positions encourage reflux with the risk of laryngeal spasm What really matters is to raise the head of the cot. All studies of the supine-versus-prone position have neglected the important effect of gravity on reflux The ideal sleeping position is with the head raised[5] but if babies must lie flat, the side is probably safer than the front or back Better still, babies' cot mattresses should be wedge shaped.

Many parents are very worried by the risk of a cot death even if they do not voice their fears The recommendations I have used for many years are:

- Lay your baby to sleep on one or other side, never the front or back
- Prop up the head of the cot by 10–12 cm (4–5")
- Keep the cot beside your bed in the first six months
- Learn to give the kiss of life
- Get medical advice if your baby is unwell

A nationwide campaign to reduce cot deaths is undoubtedly long overdue. However if it is to succeed, it is important that the recommendations are simple, sensible, and sound. I am seriously concerned about the widely publicised FSID and Department of Health guidelines.

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1 Foundation for the Study of Infant Deaths. *Reduce the risks of cot death.* London: FSID, 1992
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Imposed upper airway obstruction in small children

Sɪʀ,—Surveilance of one of the 14 cases described by Samuels and his colleagues[1] was undertaken in the department of child health in this hospital with their advice and support. In addition to the videos they describe, we recorded sound as well and found this to be of considerable importance. Although perpetrators do not know that they are being watched, they are certainly aware of the possibility of being interrupted by someone entering the room. They may go to considerable lengths to disguise what they are about and this was certainly true in our case As a result, it may not be easy to demonstrate what is happening on video alone. Some of the most compelling evidence which led to a successful outcome of the case arose from the ability to compare what we could see being done to the child with what the perpetrator was saying at the time. In addition, the audible change in a child's cry as the airway is obstructed is unmistakable even if the way in which that obstruction is being achieved is subtle.

Samuels and his colleagues describe the very careful preparation required for covert video surveillance. I would also emphasise the importance of continuing support for all the professionals involved, be they doctors, nurses, or police officers. Surveillance may be necessary for many days—all involved are only too well aware of the possible consequences of a few moments inattention, of any failure of communication, or indeed, of inadvertently betraying to the perpetrator that surveillance is being undertaken

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1 Samuels MP, McClaughlin W, Jacobson RR, *et al.* Fourteen cases of imposed upper airway obstruction. *Arch Dis Child* 1992,67:162–70

ABC of child abuse

Sɪʀ,—Torn frenula in children have been said to be 'virtually diagnostic' of non-accidental injury (NAI) [1] However, two recent cases indicate that this is not always so.

The first case was a 1 year old boy, whose sister was attending our casualty department for an unrelated reason. The boy was walking around the waiting room and fell flat onto his face. Examination of the crying child revealed a torn frenulum of the upper lip. The whole incident was witnessed by professional nursing staff and so the innocence of the incident cannot be doubted.

The second case involves the 14 month daughter of the author. After attempting to climb a vegetable rack, my daughter fell backwards, pulling the vegetable rack onto herself. Rapid investigation of the source of the subsequent bleeding confirmed my worst fears—she had a torn frenulum of the upper lip, presumably where it had been caught on the wire basket. I'm afraid that readers will have to take my word as to the innocence of this injury (what self respecting paediatrician would ever dare take such an injury to their local casualty department!) A torn frenulum is classically said to occur when a bottle or spoon is forced into the mouth of a child.[2] This association is probably strong enough to warrant the usual inquiries by the child protection agencies to see if NAI has occurred. However, before guilt of the child carers is assumed, it should be borne in mind that a torn frenulum is no more pathognomonic of

NAI than reflex anal dilatation is of child sexual abuse [3]

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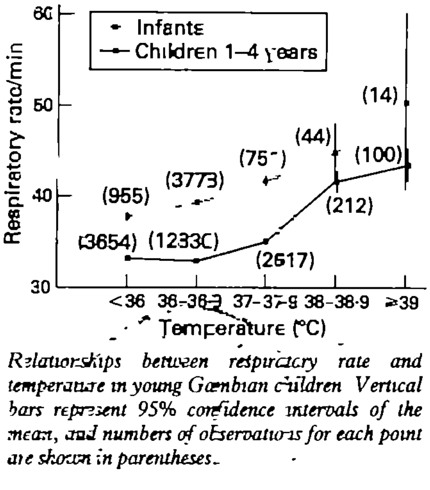
1 Speight N ABC of child abuse non-accidental injury *BMJ* 1989;298:879–81
2 Forfar J, Arneil G *Textbook of paediatrics*. Vol 2 Edinburgh Churchill Livingstone, 1984 1899
3 Bamford F, Roberts R. ABC of child abuse child sexual abuse II *BMJ* 1989,299:377–82.

Effects of body temperature on respiratory rate in young children

SIR,—Dr Simoes and colleagues have reported studies of variability in measurements of respiratory rate in young American children, but did not consider possible effects of body temperature on these measurements [1] Previous work suggested a weak association between body temperature and respiratory rate in young infants studied in Australia and Britain [2] Current World Health Organisation guidelines for the management of acute respiratory infections in children recommend that young children with cough or difficult breathing and raised respiratory rate should be treated for pneumonia irrespective of temperature.

In a community study of acute respiratory infections undertaken at the MRC Laboratories in the Gambia, weekly measurements of temperature and respiratory rate were made on a population including approximately 500 children under the age of 5 years, over a one year period. This study is described in detail elsewhere.[3] Although these repeated observations are technically not independent, we consider that measurements of respiratory rate and temperature carried out not more than once weekly on a young child may reasonably be assumed to be independent. A total of 25 025 observations on 635 young children were made. In 70 instances abnormalities on chest radiography were found and these observations have been excluded from the following analysis The relationships between temperature and respiratory rate for infants (5542 observations), and for children aged 1 to 4 years (19 413 observations), are shown in the figure. In both groups, mean respiratory rate shows a steady increase with increasing temperature of approximately 2·5/min °C over the temperature range shown A similar analysis restricted to children with cough (2537 observations) showed a similar relationship (data not shown)



Relationships between respiratory rate and temperature in young Gambian children Vertical bars represent 95% confidence intervals of the mean, and numbers of observations for each point are shown in parentheses.

The data presented, in accordance with experimental results on the effects of temperature on breathing,[4] suggest that raised respiratory rates may be partly attributable to increases in body temperature. We earlier reported that in children with cough or difficult breathing respiratory rate is a valid predictor of the presence of clinical or radiological pneumonia [3] The findings presented here do not challenge this, but they suggest that this relationship between fever and respiratory rate may account for some of the false positive diagnoses of pneumonia in children with cough or difficult breathing, fever and raised respiratory rate. This issue may be of particular importance in areas in which malaria is prevalent as it has been shown that there may be a very substantial overlap of clinical presentation in children with malaria and pneumonia [5] The possible effect of this phenomenon on the specificity of raised respiratory rate as an indicator for pneumonia needs further investigation.

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1 Simoes EAF, Roark R, Berman S, Esler LL, Murphy J Respiratory rate measurement of variability over time and accuracy at different counting periods *Arch Dis Child* 1991;66: 1199–203
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5 Bloland PB, Redd SC, Kazembe P, *et al* Co-trimoxazole for childhood febrile illness in malaria-endemic regions *Lancet* 1991;337. 518–20

Consumer safety and child choking attacks

SIR,—From time to time you publish letters which do not have any direct relevance to immediate past publications and it would be helpful if such letters indicated their origin. One such letter recently published gives no explanation as to why Drs Matthes, Sibert, and Levene were concerned about possible inhalation of foreign bodies from toys.[1] Those paediatricians who help local authority consumer protection departments by assessing or commenting on the safety of toys will be aware there has been a recent increase in the vigilance of trading standards officers regarding choking hazards to children because of a number of deaths Dr Levene chaired a working party under the auspices of the Child Accident Prevention Trust, which found little published evidence of any serious hazard from the inhalation or ingestion of hair plucked from toys.[2] This report is being used by manufacturers to defend their products against legal action even though safer alternative materials are available.

The recent letter refers to a survey of paediatricians and ear, nose, and throat surgeons throughout Wales seeking to identify their awareness of choking hazards to young children from hair or other small objects It is gratifying that they knew of no such hazard but we suggest that the wrong people were asked the wrong questions. The children who died in Leeds (from obstructive inhalation after ingestion of hair from a toy donkey) and in Birmingham (after inhalation of a small piece of plastic from inside a novelty chocolate egg) were unknown to paediatricians or ear, nose, and throat surgeons because casualty doctors and pathologists dealt with them.

Life is full of hazards and it would be impossible to ever legislate them all away. Even if this could be done it would then so grossly distort normal childhood experience as to be unacceptable There are, however, measures that can be taken to control unnecessary hazards and we are of the opinion that inappropriately long hair that is inadequately fixed to a fur fabric is not suitable for the exterior decoration of any toy. It is to be expected that young children will pluck or suck the hair and may then inhale or ingest with the risk of asphyxiation or bezoar formation. Small pieces of plastic that may occlude the airway are also inappropriate in toys intended for young children.

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1 Matthes J, Sibert J, Levene S. Children choking on foreign bodies from toys *Arch Dis Child* 1991;66:1104.
2 Levene S. *Hair on toys—what is the hazard?* London Child Accident Prevention Trust, 1988.

Coroners' records of accidental deaths

SIR,—Dr Levene has demonstrated the potential of using coroners' records as a source of data relevant to child accident prevention studies.[1] In a similar retrospective study in this district using the coroner's records we discovered 69 children aged under 15 years who had died as a result of an accident between the years 1980–9 inclusive. Road traffic accidents represented the commonest fatal accident with falls, drownings, and asphyxia accounting for the remainder. Head injury was the commonest reported cause of death. Most deaths occurred within 2 km of the child's home while children were playing without supervision. We encountered an association between social class and incidence of accidents with 10 times as many accidents occurring in classes IV and V than in I and II. There was, in addition, a clustering of cases in areas with high deprivation scores.

This information was of great use to us in planning local child accident prevention strategy as it enabled us to target limited resources to areas where they were needed most. However, as in Dr Levene's case, we were made aware of the limitations of using coroner's records alone for this purpose. We discovered that inquisitions relate to deaths occurring to children who died within the boundaries of our district only During the period of our study we became aware that several local children had died while visiting other districts but this information would not

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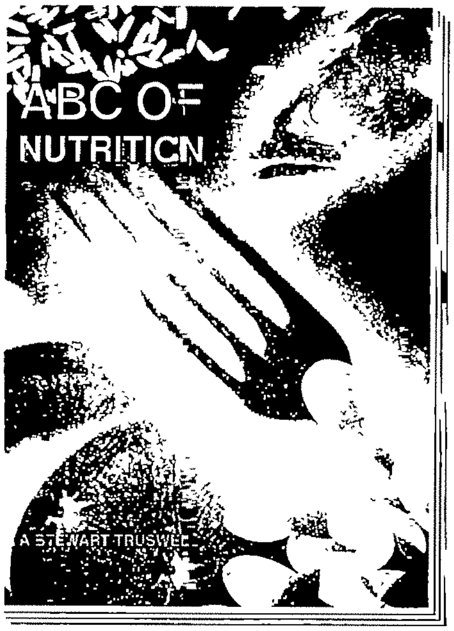

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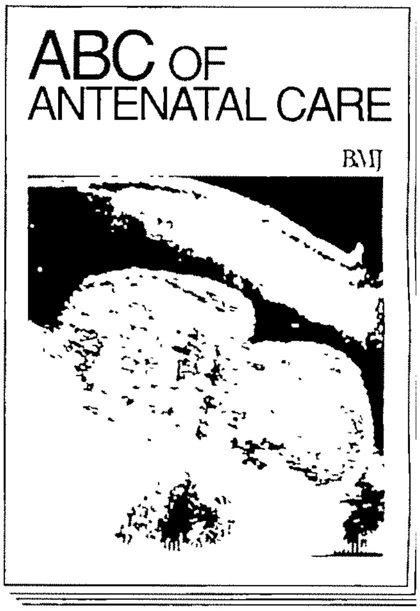

Healthy women with normal pregnancies need little formal care; those at risk of damage to their own or their baby's health need the best of scientific medicine. The aim of antenatal care is to distinguish between these two groups, giving those who need it the full range of diagnostic and therapeutic measures while avoiding unnecessary intervention in those whose pregnancy proceeds normally. In the *ABC of Antenatal Care* Geoffrey Chamberlain, professor and chairman of the department of obstetrics and gynaecology at St George's Hospital Medical School, London, outlines the practicalities of routine antenatal care and the management of the major medical problems that may arise. Originally published as a series of articles in the *BMJ*, this manual discusses with common sense and humour the background to current practice and indicates how it could be improved in the 1990s.

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under normal circumstances be recorded by our local coroner's office. In our efforts to resolve the difficulty, we encountered a more complete but less detailed source of data. In those districts where child health surveillance and school health records are computerised, a comprehensive list is kept of children who have died in order that grieving parents are not inadvertently sent invitations to attend child health surveillance appointments. The list is usually complete and includes local residents who have died outside of the district boundaries. The information contained in these lists usually just extends to the child's name, address, and cause of death with no further details. However, we found these records of use in supplementing data supplied by the coroner's records.

We would concur with Dr Levene in her plea for a comprehensive prospectively compiled childhood accident mortality database. Coroners' inquisitions and child health records will yield basic data which might, perhaps, be usefully supplemented by confidential inquiries into the circumstances of individual accidents. Collation of locally relevant data is a key element in child accident prevention which should be a priority for every health authority.

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1 Levene S. Coroners' records of accidental deaths. *Arch Dis Child* 1991,66:1239–41

Subdural fat effusion complicating parenteral nutrition

SIR,—Rushforth *et al* recently reported an unusual complication of parenteral nutrition via a Silastic catheter.[1] They stated the catheter was probably in the external jugular vein presumably based on a plain film of the head and neck.

It seems to me that this assumption is unfounded, principally because the catheter would not advance past 9 cm. In my experience this is caused by the catheter wedging in a small vessel. It would thus seem more likely that the catheter had found its way via the deep temporal vein into the anterior diploic vein with free communication to meningeal veins [2] Rupture of these veins would result in a subdural collection

In my opinion the message of the paper of Rushforth *et al* should be that if a Silastic catheter will not advance, it is probably wedged in a small vein The catheter should therefore be withdrawn 1 or 2 cm before readvancing If this fails the tip should be left one centimetre proximal to the site of obstruction and thus presumably in a larger vein.

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1 Rushforth A, Green MA, Levene MI, Puntis JWL. Subdural fat effusion complicating parenteral nutrition. *Arch Dis Child* 1991,66: 1350–1.
2 Williams PL, Warwick R. Cranial and intracranial veins. *Gray's anatomy* 36th Ed. Edinburgh Churchill Livingstone, 1980

Dr Rushforth and colleagues comment:

We note Dr Jones' suggestion of a possible route of a percutaneous central venous catheter, via diploic veins, to lie in the middle meningeal vein to explain a subdural collection. However, the diploic veins are absent at birth and do not develop until around 2 years of age [1] The infant in the case report was still less than 37 weeks' corrected gestational age at the time of the incident.[2]

It may be possible to suppose passage of a catheter via an emissary vein to lie in the sigmoid sinus. However, this route is tortuous and would not be supported by the appearance on the original radiograph.

We agree that if a catheter will not advance, it is probably lodged in a small vein and should be withdrawn. Free flow of blood back through the catheter would support its tip being in a large vein, as the case in our report.[2] However, the ideal position for central venous catheters should be the right atrium where risk of retrograde flow is less.

1 Williams PL, Warwick R, Dyson M, Bannister LH, eds Angiology. *Grays anatomy* 37th Ed. London Churchill Livingstone, 1989 798–805.
2 Rushforth A, Green MA, Levene M, Puntis JWL Subdural fat effusion complicating parenteral nutrition. *Arch Dis Child* 1991,66: 1350–1.

Health for all children

SIR,—The importance of early diagnosis of biliary atresia has been stressed repeatedly by hepatologists and is now acknowledged by those responsible for child health surveillance programmes.[1] However, it does seem premature to suggest that we should change the age at which the infant's first formal postnatal review is performed,[2] particularly as the revised programme of child health surveillance recommends that this review should be combined with the first immunisation at the age of 8 weeks.[3]

Each district in the UK will produce one new case of biliary atresia every four or five years. We need to know what strategies would be best to achieve early detection of such a rare condition Formal screening may be less effective than professional education combined with easy rapid access to the appropriate tests and the expertise to interpret them. The paediatric hepatology team at King's College Hospital is uniquely well placed to determine what work load would result, and what unforeseen problems might arise, if the various strategies they propose were to be implemented. Our experience with neonatal screening for hearing loss has taught us how much effort and commitment are required to make such programmes work effectively, even when run by an enthusiast.

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1 Hall DMB *Health for all children* 2nd Ed. Oxford: Oxford University Press, 1992 44
2 Hussein M, Howard ER, Mieli-Vergani G, Mowat AP. Jaundice at 14 days of age exclude biliary atresia *Arch Dis Child* 1991,66:1177–9
3 Hall DMB. *Health for all children*. 2nd Ed. Oxford Oxford University Press, 1992 125–6

Intraosseus infusion

SIR,—The intraosseous route for emergency infusions of fluids and drugs is underutilised in this country and Drs Ryder, Munro, and Doull do well to remind us of its simplicity and efficacy when vascular access is difficult and speed essential.[1] However, when discussing the various sites for intraosseous infusion they include the sternum. This site is too hazardous to recommend in my opinion. The upper tibial shaft is safe and favoured as the intraosseus infusion site of first choice by most emergency physicians. The lower end of the femur or humerus are other useful alternatives.

Specially designed intraosseous needles are available and have a shelf life of approximately five years. Their advantage over using hollow shafted needles (for example a large butterfly or needle of large bore intravenous cannula) is that they are less likely to become blocked by bone particles and can more easily be anchored in situ. Their cost is not prohibitive (about £10–£15 each) and it would seem appropriate for all emergency trolleys or boxes to include such needles. One size, either a 16 or 18, is usable in most situations for all ages of children

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1 Ryder IG, Munro HM, Doull IJM Intraosseous infusion. *Arch Dis Child* 1991,66:1442–3.

Familial asplenia

SIR,—We read the article on haemophilus septicaemia in congenital asplenia[1] and the subsequent correspondence[2 3] with great interest We would like to describe our experience, which illustrates the importance of familial asplenia and also a potential disadvantage of not performing a necropsy.

A 21 month old girl, the second child of non-consanguineous white Australian parents, presented to a peripheral hospital with a short history of fever and delirium. She was profoundly shocked with widespread purpura and ecchymoses. A presumptive diagnosis of meningococcaemia was made, resuscitation with artificial ventilation, antibiotics and plasma was commenced, and transfer to this hospital was requested. On arrival here she was moribund and died within minutes. Blood cultures were sterile. Necropsy was requested but declined by the distraught parents.

The parents subsequently had a third child, a boy, who presented at the age of 4 months with fever and rapid onset of shock and purpura. He was found to have purpura fulminans, with confluent ecchymoses of his distal limbs, ears and nose, and with purpura on his lips Cultures of blood and cerebrospinal fluid grew *Streptococcus pneumoniae*. Blood films showed numerous erythrocytes containing Howell-Jolly bodies. An ultrasound scan revealed no spleen and asplenia was confirmed by technetium scan. Cardiac ultrasound scan was normal. His sister's original blood film was retrieved from the peripheral hospital and the red cells were also found to contain many Howell-Jolly bodies. The oldest child is well, has a normal peripheral blood film, and has a spleen on ultrasound.

The patient required intensive resuscitation with artificial ventilation, colloid, blood, and inotropes. He developed peripheral gangrene, requiring amputation of the fingers but not thumb of his left hand to the metacarpophalangeal joints, amputation of his right fingers to the proximal interphalangeal joints, amputation of all his toes, and removal of necrotic tissue and bone on his left heel. He had extensive skin grafting to the lower limbs Good function of his right hand was predicted He was discharged on prophylactic antibiotics. Polyvalent pneumococcal vaccine and meningococcal vaccine will be given at 24 months and conjugate vaccine against *Haemophilus influenzae* type b as soon as it is available in Australia.

These siblings presumably have recessively inherited congenital asplenia and normal hearts. Hereditary splenic hypoplasia was first described in three of five siblings by Kevy *et al*.[4] In a review of 60 children with asplenia or polysplenia from Toronto, there were two families in which two siblings had isolated asplenia and one family in which two siblings had polysplenia

It was assumed that our first patient died of meningococcal sepsis, although in retrospect she may have had pneumococcal sepsis, as both organisms may sometimes fail to grow from severe cases. In an ideal world a necropsy would have been performed, would have revealed asplenia and we would have screened the next child at birth. Prophylactic antibiotics have been shown to be effective in reducing the incidence of bacterial sepsis in children with congenital asplenia,[6] and immunisations as already described could have been given at the appropriate age

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Growth performance of affluent Indian children under 5 years of age

SIR,—Paediatricians interested in the growth patterns of children of families originating from the Indian subcontinent may like to know of a study by the Nutrition Foundation of India on 'Growth performance of affluent Indian children (under fives)'.[1] The study was undertaken to determine whether the international growth standards developed by the National Center for Health Statistics in the USA were applicable to Indian children. A corollary to this was the desirability, or otherwise, of collecting data on Indian children on a national scale

The authors accepted that socioeconomic and environmental factors and the malnutrition-infection complex rather than genetic factors were the main constraints determining the differences between the growth performance of children in developed and developing countries.[2] In order to eliminate these factors as far as possible, only children from affluent families (they took some pains to define 'affluent') were studied in seven cities: two in the north (Ludhiana and Delhi), two in central India (Kota and Varanasi), one on the west coast (Bombay), one in the south (Bangalore), and one on the east coast (Calcutta).

The results showed that 'affluent' children (0–5 years) in Ludhiana and Delhi in the north had attained a level of growth in height and weight which nearly corresponded to those of the international growth standards and it was therefore concluded that these standards could be used for Indian children In the remaining cities where growth fell below the American standards it was thought that the explanation lay in the dietary differences between the various parts of India.

The value of this study is that paediatricians in Britain can use (or continue to use) the American or the Tanner-Whitehouse standards for the children of Indian origin in the important 0–5 year period It must be emphasised, however, that these findings do not apply to the neighbouring countries of Pakistan, Bangladesh, Nepal, and Sri Lanka. Those interested in the details of the study should consult the original report.

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1 Agarwal KN, Agarwal DG, Benakappa SM, *et al*. *Growth performance of affluent Indian children (under fives)* New Delhi Nutrition Foundation of India (scientific report 11), 1991 (Available in the Library of the Royal Society of Medicine, London)
2 Anonymous. A measure of agreement on growth standards [Editorial] *Lancet* 1984,i:142–3

Birthweight ratio in public health

SIR,—A similar birthweight ratio to that used for guidance in sophisticated neonatal intensive care discussed by Dr Lucas *et al*[1] has been suggested as a public health indicator This was termed the 'socioeconomic birth weight [b wt] quotient' (or ratio).[2] It was defined as:

$$\frac{\text{average b wt low socioeconomic population}}{\text{average b wt upper socioeconomic population}} \times 1000$$

It was considered as a rough potential cumulative measure of 'social development', especially of prenatal care, maternal nutrition, and infections (notably placental malaria[3 4]).

This approach is only valid when the community concerned is, in general, genetically uniform Also, as always with such comparisons, problems occur in defining the two groups Generally well nourished, genetically homogeneous communities with good prenatal services, as in Denmark, should have an index of 1000. In a study in an area in India, results ranged from 872 to 885.[5]

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1 Lucas A, Morley R Birthweight ratio *Arch Dis Child* 1991,66:1099
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Toxic shock-like syndrome due to *Streptococcus pyogenes*

SIR,—Streptococcal toxic shock syndrome has been recently reported in both adults[1–3] and children.[4] Torres-Martinez *et al* described four children all of whom survived but required intensive treatment and aggressive cardiovascular resuscitation.[5] Reports in adults have often demonstrated less favourable outcomes despite appropriate management Our recent experience with one child would agree with this.

A previously well, 5 year old boy was admitted to Crawley Hospital with a two day history of cough and sore throat He developed inspiratory and expiratory stridor three hours after admission becoming distressed and requiring nasotracheal intubation. The epiglottis was normal but there was evidence of a tracheitis; a tracheal aspirate grew group A β haemolytic stretococcus but blood cultures were negative He was given intravenous benzylpenicillin, flucloxacillin, and cefotaxime Thirty six hours later he was extubated but after 12 hours he suddenly deteriorated and required reintubation At that time a chest radiograph showed partial collapse of the left lower lobe. He was transferred to the Royal Alexandra Hospital for Sick Children at Brighton for further management and on arrival 72 hours after his original hospital admission his condition was stable. His full blood count, haemoglobin, urea, and electrolyte concentrations, and blood gases were all normal. His blood pressure was 100/50 mm Hg. Intravenous benzylpenicillin was continued in a dose of 150 mg/kg/day in four divided doses and after discussions with the microbiology laboratory gentamicin 40 mg every eight hours and chloramphenicol 500 mg every six hour were added. A chest radiograph shortly after admission showed considerable improvement. Twelve hours after admission, while fully ventilated, he suddenly became hypotensive, bradycardic, and hypoxic, the deterioration being associated with evacuation of his bowels. The heart rate fell from 120 to 40 per minute and the oxygen saturation from 96 to 40%. Despite 80 ml/kg of colloid followed by a continuous infusion, intravenous adrenaline 2 ml of 1:10 000×3, a dopamine infusion, and intravenous atropine 200 μg×2, he deteriorated further His liver enlarged to 5 cm below the right costal margin and he developed disseminated intravascular coagulation and renal failure. He died 17 hours later. Postmortem examination revealed only a hyperaemic trachea and bronchi There were small bilateral pleural effusions. The National Reference Laboratory (Colindale) reported an antistreptolysin-O titre of 400 units/ml, an anti-DNAse B titre of 180 units/ml, and an antihyaluronidase activity of 1024 units/ml. The streptococcus isolated from the tracheal aspirate was sensitive to penicillin, erythromycin, and cefotaxime.

Despite aggressive intensive care and adequate antistreptococcal antibiotic treatment, toxin release may occur late in the illness and have a fatal outcome.

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Gastrointestinal complications associated with dexamethasone treatment

SIR,—While the recent reports of gastrointestinal complications in preterm babies receiving dexamethasone for bronchopulmonary dysplasia emphasise the need to observe these babies with ever greater vigilance,[1 2] it is worrying to note that perforations can also occur 'silently' and escape clinical recognition. Unlike most of the babies described in these reports, who rapidly became unwell and required vigorous resuscitation, we recently had a case who developed duodenal perforation eight days after dexamethasone treatment for chronic ventilatory dependency and yet the abdominal signs evolved insidiously over two days with remarkably little respiratory, haemodynamic, or metabolic embarrassment to the baby and the presence of free air in the peritoneum was detected only after a routine radiograph.

It is possible that this baby tolerated the perforation better because she was being ventilated, albeit with low rates and inspiratory pressure, and was therefore better able to cope with the splinting of the diaphragm by the pneumoperitoneum. At the same time, it is also possible that dexamethasone modified the abdominal signs, as has been described in adults.[3 4] These observations merit attention especially as a number of studies designed to look into the efficacy of dexamethasone in neonatal respiratory distress syndrome are already on the horizon. We also feel that while the temporal relationship with dexamethasone treatment in the above cases was more than coincidental, there are many other factors present in this subset of population known to predispose to gut ischaemia and perforations, which should be included in the analysis while calculating the benefit:risk ratio of steroid treatment.

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1 Ng PC, Brownlee KG, Dear PRF Gastroduodenal perforation in preterm babies treated with dexamethasone for bronchopulmonary dysplasia. *Arch Dis Child* 1991,66:1164–6
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Misuse of the English language

SIR,—I have just perused your September issue, and with tongue only slightly in cheek, write to enlist your help in a campaign similar to our joint efforts to stamp out duplicate publication. I refer to the defence of our language, which we colonials inherited from you several centuries ago.

Although I really appreciated the papers on heart-lung transplantation, which seem to have been written more honestly than most articles on transplantation on this side of the Atlantic, I was distressed to note that every writer referred to the 'transplanted children', rather than 'the children with transplants'. As I am fond of saying, organs, not children, are transplanted. This error is being perpetuated in many journals; I hope that you will help us correct it.

My second concern has to do with the misuse of the word 'regime' when 'regimen' is intended. I found this at least twice in your September issue.

I often comment to our junior faculty members that the British are to be admired for their succinct style in writing for medical journals. Thus, I hope that you will join us as we stand, like Horatio, fighting overwhelming odds in the defence of our difficult language.

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The technical editor comments:
Point(s) taken!

Sister journals

SIR,—In some quarters it will be seen as worthy of a good giggle, in others disingenuous of David Mellor to confess that his school French 'has not really been kept fresh . . . from occasional holidays in French gîtes . . .' and at the same time to complain of examples of poor translations (into English) of titles and summaries in *Archives Françaises de Pédiatrie*;[1] and then to continue with 'Clearly (that journal's) parochiality must be largely to do with the difficulty non-Francophones have writing in that language'. As a fervent francophile and part time resident in France, the parochiality does seem to be on the other foot when he suggests that all the other 'European medical journals should be encouraged to become fully bilingual (that is, national language *plus English*)'! (my italics and exclamation mark)

He is right to say that highly skilled medical translators will be in great demand, as non-medical linguists are notoriously unreliable in the language of doctors. As one who has a vested interest in recreating the *entente cordiale*, however, and who sympathises with the widespread French resentment at British arrogance in insisting on our own language, I do hope colleagues will become more sensitive in their Archival writings by 1992!

Did Dr Mellor notice the full page advertisement for the *Organ der Deutchen Gesellschaft fur Kinderheilkunde*, entirely in German, on the page immediately after his piece? *Gott in* . . . .!

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1 Mellor DH Sister journals—France *Arch Dis Child* 1991,66:1364.

Dr Mellor comments:
La plume du professeur est plus puissante que l'épée.

The geneticist's dilemma

What should be the aims of clinical genetics? To promote the welfare of those with genetic disease? To offer genetic counselling? To offer prenatal diagnosis and selective termination of pregnancy? To prevent genetic disease? It might be thought that each of these aims would be laudable in certain circumstances but there is perceived to be a dilemma in so far as the first and third of these aims might be thought, on occasions, to be antagonistic. The problem is discussed in a recent paper in the *Lancet* (Angus Clarke, 1991;**338**:998–1001).

Can a doctor truly respect people who have a genetic disease and at the same time offer termination of pregnancy when that disease is diagnosed antenatally? In some cases I believe he(she) can and so does Dr Clarke. He gives as examples severe mental retardation such that the person is socially unaware, and severe and progressive disorders such as Duchenne muscular dystrophy. He is concerned, though, that the extension of therapeutic abortion to less severe disorders such as neurofibromatosis or Turner's syndrome automatically implies that such people are devalued in the eyes of society. It seems at first sight an absurdity for the same doctor to *care* (in both senses of the word) for such people and yet to work to prevent others like them being born. But is it really absurd? Did the introduction of polio vaccine *devalue* people paralysed by poliomyelitis? I don't believe that many people would suggest so. Is there any real difference *in logic* between 'We are going to immunise babies to prevent people being like you' and 'We are going to terminate pregnancies to prevent people being like you'? The only difference, it seems to me, is the difference between immunisation and therapeutic abortion and the issue of the sanctity of life of the fetus. It is not absurd to say, 'You have a problem. I like and respect you but I think that other people would prefer not to have the problem'. If that is accepted, and Dr Clarke does accept it in the case of severe genetic disease, then the issue becomes not the desirability of prevention but the acceptability of the means. Most people, wherever they stand on the 'sanctity of life' issue, feel unease, great or small, about termination of pregnancy and would not accept its use for relatively minor conditions, and, as Dr Clarke points out, the psychological repercussions of termination may cause greater anguish than the disease under consideration. So the means must be balanced against the aims. The prevention of any condition that causes distress is a laudable aim but the means may be unacceptable. Termination of pregnancy to prevent dental caries would have few proponents but those who oppose fluoridation of water supplies do so not because they consider the prevention of caries to be an improper aim but because they object to the 'contamination' of the water supply as the means.

Dr Clarke's second point is to question the validity of 'non-directive' genetic counselling as regards antenatal diagnosis and termination of pregnancy. It is currently part of the philosophy of clinical genetics that the geneticist gives the facts and the 'clients' make the decisions. Can that be true? Doesn't the offer of prenatal diagnosis and termination imply that the geneticist is prepared to accept that termination is morally justifiable for the condition in question? The geneticist can no more act in a moral vacuum than anybody else. There may be a need to reassess the work of clinical geneticists, with more involvement in the care of people with genetic disease, an acceptance that antenatal diagnosis is always directive to a greater or lesser extent, and some attempt to reach a consensus about which conditions justify termination of pregnancy and which do not.

ARCHIVIST

Archives of Disease in Childhood 1992, 67: 669–674

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Annotations

Paediatric cochlear implantation

In 1986, William House, one of the pioneers of cochlear implantation wrote, 'Cochlear implants have now reached a robust childhood'.[1] This quotation is particularly apposite today with cochlear implantation being more widely offered to profoundly deaf children. More than 800 children worldwide have now received the Nucleus multichannel device, one of the most widely used of the implants currently available.

The concept of electrical stimulation of the auditory system dates back to Volta[2]; the recent history of cochlear implantation has been summarised by Luxford and Brackman.[3] It is really only in the last decade that cochlear implantation has moved from the experimental field into wider clinical application.

What is a cochlear implant?

In essence a cochlear implant is a very sophisticated (and somewhat expensive) hearing aid, bypassing the inner ear hair cell system and stimulating the ganglion cells of the VIIIth nerve directly.[4] The basic components of any cochlear implant system comprise a microphone which is connected to an externally worn speech processor which filters speech and extracts formant information. These data are transmitted to the receiver/electrode package which is the implanted part.

An implant may be extracochlear, stimulating the nerve via an electrode positioned adjacent to the round window, or it may be intracochlear, the electrode(s) being inserted into the lumen of the cochlea. Implants may be single channel, such as the UCH/RNID device[5] or they may be multichannel such as the Ineraid[6] or Nucleus[7] devices. The Ineraid uses a transcutaneous electrical connection, the Nucleus depending on electromagnetic induction for transmission of the signal to the implanted package. Intracochlear multichannel devices provide significantly greater benefit than single channel ones and are, therefore, the treatment of choice.[6 8 9]

Indications for paediatric cochlear implantation

Cochlear implantation is indicated for profound sensory (cochlear) hearing loss; it depends on the integrity of the cochlear nerve. In the UK the prevalence of severe or profound sensorineural deafness in children is between one and two per 1000.[10 11] It is only a small proportion of such children that is likely to need cochlear implantation as the majority can be helped by suitable conventional hearing aid systems, coupled with appropriate habilitation or rehabilitation. While the detailed audiological criteria for implantation in children may vary in different centres, there appears a broad consensus that the child needs to have had an adequate trial of suitable conventional amplification. In the Federal Food and Drug Administration (FDA) programme administered in 24 centres in the USA, and in the Melbourne programme in Australia, the criteria include auditory thresholds of greater than 90 dB averaged over 500 Hz, 1 kHz and 2 kHz, *aided* auditory thresholds of 55 dB or greater, or speech perception scores of less than 20% using standard sentences prepared by the Central Institute for the Deaf, USA.

In the Nottingham programme our criteria include total loss of hearing with aided responses at thresholds greater than 80 dB across the frequency range from 500 Hz to 4 kHz. In the light of others' experience this latter criterion has been relaxed to aided thresholds of 70 dB, although to date no child has been implanted using that new criterion.

Much debate has centred around the question of whether to implant prelinguistically deaf children or only those who have had some experience of language. In the FDA trials 64% of those implanted were deafened at or before 24 months of age and are considered prelinguistic, with 43% being congenitally deaf.[12] In Nottingham we have moved more cautiously: of a total of 20 children who have undergone this surgery, only two have had a congenital hearing loss although a further eight belong in the prelinguistic category. Encouraged by our early assessment of the progress of these two children, and in the light of results from other centres, we have now elected to include within our criteria congenitally deaf children under the age of 5 years.

Special needs of children

ASSESSMENT

Considerable skill is needed in evaluating not only the hearing of young children but also their spoken language and other communication skills.[13] Conventional tests of spoken language may be used for children with functional language, while in the preverbal stage video analysis of a child with a known adult may be used,[14] both before and after implantation. Behavioural audiometry results should be supported by those from evoked response audiometry.

As well as an auditory assessment, in our programme the child also undergoes general medical and otological evaluation, including radiological assessment using computed tomography. The child should be generally medically fit and there should be no active middle ear infection. A computed tomogram is an important element in the assessment process; in cases of deafness due to meningitis, labyrinthitis ossificans (new bone growth within the lumen of the cochlea) may occur and prove a contraindication to implantation of an intracochlear device. Congenital inner ear malformation may be demonstrated, such as Mondini dysplasia or abnormalities of the internal auditory meatus.

Finally, in assessing a child for possible implantation, the expectations of the parents need to be taken into consideration; these should be realistic. Time must be allocated in the evaluation phase for counselling the parents; they need to be aware of the long road ahead if their child undergoes implantation. The rehabilitation period is a very long one. It is essential that appropriate rehabilitative support be available locally for the child and that the potential as well as the limitations of the implant should be known to the local teacher(s) of the deaf.

SURGERY

Implantation in children poses special challenges. Preparation of the child is all important, and close involvement of the parents is essential. It is helpful to have shared photographs and books about children previously implanted. If the deafness has resulted from meningitis then the operative period may prove particularly distressing for the family. Sensitive preoperative counselling may do much to help reduce the stress.

The surgical incision should be planned so as to be well away from the actual implant. The squamous temporal bone is much thinner in a child and special caution needs to be exercised when fashioning the bed for the implant package. The remainder of the surgery is little different from adult implantation.

In the postoperative period seemingly simple matters such as suture removal may prove very traumatic and the Nottingham team has now adopted the use of absorbable subcutaneous sutures.

Children are in hospital for only two or three days postoperatively, which is no different from any other major middle ear surgery. Postoperative vertigo has not been encountered in any of the children in the Nottingham programme.

TUNING AND REHABILITATION

Each electrode of the multichannel array has to be tuned to obtain threshold levels and upper, comfort, levels. Again, as with preoperative evaluation, this requires the specialised skills of those used to assessing young deaf children. The initial reaction of many children to the initial switch-on is to burst into tears; careful preliminary counselling will avoid distress to the parents from this. Tuning can be a very time consuming process, and it is hoped that current work involving peroperative measurements of electrically evoked stapedius reflex levels and brain stem auditory responses will help reduce this.

After the initial tuning, the process of auditory rehabilitation starts. The skills of the teacher of the deaf become paramount, not only in direct contact with the child but also in involving many others in this process, including parents and other members of the family, other teachers, and many more who come into daily contact with the child.

During the rehabilitation period, there is regular assessment of communication skills and also language development, the latter involving the skills of the speech therapist.

It will have become obvious from the foregoing that paediatric cochlear implantation demands a team approach at all stages, involving audiologist, otologist, teacher(s) of the deaf, speech therapist, medical physicist, radiologist, and not least the child and his or her parents and other family members.

Special benefits to children of cochlear implantation

The benefits of cochlear implantation in children may be greater than those for adults. Loss of hearing in young children is likely to result in failure to develop, or loss of already developed speech and language. Hearing is essential for this development. Mecklenburg *et al* have listed the benefits as primary and secondary (table 1).[15]

There may also be tertiary effects, with benefit to education and intellectual development and longer term employment prospects. The costs of cochlear implantation may be offset against reduced educational costs, reducing the additional costs of placement of a child in a special school for the deaf. The concept of the developmental critical period has become important in the past decade,[16] with anatomical and metabolic changes in some brain stem auditory nuclei being demonstrated.[17] Loeb notes that language acquisition, whether verbal or visual, is greatly compromised if training is not begun early.[16] He comments that if critical periods exist in the development of auditory perceptive capabilities, this would introduce an urgency into the decision of whether to implant devices (that are now primitive but rapidly evolving).

While there is a clear trend towards continued improvement in performance with longer term use of implants, it remains to be seen whether prelinguistically deaf children will continue to progress, although preliminary evidence is encouraging. In Nottingham we have seen a steady improvement in performance with time. Preoperatively none of the children receiving implantation were even aware of environmental sounds; of the seven children assessed at 12 months after operation, three could discriminate some speech without lip reading and four could understand speech without lip reading.

Paediatric cochlear implantation in the United Kingdom

In 1989 the Department of Health and Social Security announced special funding for six centres to conduct assessment of cochlear implantation. The Nottingham paediatric cochlear implant programme received funding from this initiative, having carried out an initial five implants supported by charitable funds. The Nottingham programme is the only dedicated paediatric implant centre within the United Kingdom although a limited number of implants has been carried out in other parts of the country. Using the Nucleus 22 channel intracochlear device 19 children aged between 2 years and 10 years have received

Table 1 Benefits of cochlear implantation

Primary	*Secondary*
Detection of sound at comfortable loudness levels	Improved voice quality
Improved identification of the possible elements of speech	Improved speech production (accuracy)
Improved speech perception for closed, and open, set speech stimuli	Increased phonological repertoire
Enhanced lip reading skills	Improved single word receptive vocabulary

Table 2 Hearing before and after implantation in 20 children

Performance	*Before implant (n=20)*	*After implant*		
		Immediate (n=19)	*6 months (n=11)*	*12 months (n=7)*
Can freely use telephone				
Understands speech without lipreading			1	4
Discrimination of some speech sounds without lipreading			6	3
Understands speech with lipreading		1		
Recognises environmental sounds			4	
Responds to spoken language		11		
Aware of environmental sounds		7		
No awareness of sounds	20			

implants in Nottingham over a three year period, funding currently allowing 10 implants per year.

With increasing experience we have extended our initial criteria where implants were only given to children with an acquired hearing loss to include now those with a congenital loss. Initial audiometric criteria have similarly been relaxed, as already noted.

Of the 20 children who have so far undergone surgery, 15 of whom were deaf due to meningitis, one operation was unsuccessful due to extensive osteoneogenesis and one child has been explanted. This latter followed development of pain on stimulation and resultant failure to use the implant. No major surgical complications have been experienced and the hearing results may be summarised in table 2.

Summary

Cochlear implantation may now be considered as a method of managing children with profound sensory hearing loss who do not benefit from conventional amplification. It involves a team approach with integration of many skilled individuals, as well as the child and his or her parents and family.

As William House has said, in 1991, 'The future is not in the adult programme, but in the continued expansion of the children's programme'.[18]

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Detection of minimal residual disease in leukaemia

The advent of modern intensive treatment has ensured that the majority of children with acute lymphoblastic leukaemia (ALL) will attain complete haematological remission. The length of this remission is, however, dependent on effective elimination of malignant cells as relapses are almost certainly due to residual leukaemic cells unresponsive to initial treatment. Such cells are referred to as minimal residual leukaemia or minimal residual disease (MRD) which is effectively the lowest number of abnormal cells identifiable with the available methods.

Detection of minimal residual disease

Remission in leukaemia is conventionally defined by a level of 5% leukaemic blasts or less in the bone marrow. However, identification of low numbers of leukaemic cells in a background of normal regenerating bone marrow precursors presents difficulties for even experienced haematologists. More sensitive and specific methods have been developed to complement morphology,[1,2] and these will be discussed.

Immunological analysis

Immunological analysis has shown that aberrant or asynchronous surface markers are often present on leukaemic cells but absent from their normal counterparts.[3,4] Two colour immunofluorescent techniques were initially developed to detect residual blasts in the bone marrow of patients with T cell acute lymphoblastic leukaemia as the phenotype CD7+/cytoplasmic CD3+/terminal transferase (TdT)+ is normally found only on thymic precursors.[5] The coexpression of the CD10 antigen on blasts from patients with 'common' ALL together with the myeloid associated antigens CD13 or CD33, or of CD10 with the T cell markers CD2 or CD7, is a useful indicator of MRD which can be exploited using two colour immunofluorescence and fluorescence activated cell sorter analysis. The technique can detect one leukaemic cell in 10^4 normal cells.[6] This technique is limited by the small numbers of leukaemias expressing such aberrant surface markers. In addition, the frequency of normal regenerating precursor cells expressing unusual combinations of surface markers has not been well studied and may be more common than realised, giving rise to false positive results.

Cytogenetic abnormalities

Consistent cytogenetic abnormalities in the malignant cells are useful markers to monitor MRD, but chromosome analysis is dependent on dividing cells, and in 'remission' marrows the 1–5% abnormal cells present may not enter mitosis, thus limiting its use. The method is labour intensive, requires fresh samples, and at least 100 cells need to be screened for each sample.

Molecular analysis

Molecular analysis provides a sensitive and specific technique to monitor MRD, particularly in cases of ALL.[1] The DNA rearrangements in the genes coding for the immunoglobulin heavy chain (IgH) in B cells, or the T cell receptor complex in T cells, can be detected in the majority of cases of ALL of T or B cell origin.[7] Detection of clonally derived cells has been shown to be useful to evaluate the remission status of patients undergoing treatment and to predict early relapse.[8,9]

B LINEAGE LEUKAEMIAS

In B lineage ALL, the IgH gene rearrangements are unique to each leukaemia and provide a tumour specific marker for individual patients. Using conventional Southern blotting, the level of sensitivity of detection of malignant cells is only 1–5% and it has not proved possible to identify all patients at risk of late relapse.[8 9] Methods to improve the sensitivity have relied on the polymerase chain reaction (PCR) to amplify very small amounts of tumour marker DNA. This can then rapidly be visualised by gel electrophoresis.[10] However, a number of problems may arise in applying PCR based techniques to the analysis of IgH gene rearrangements. IgH gene rearrangement involves the selection of one variable (V) gene out of more than a 1000 which is then joined to one of six joining (J) genes via an additional D (diversity) gene. Antibody specificity is encoded by the entire VDJ segment and the number of gene rearrangements possible is very large. As these rearrangements are thus unique to individual leukaemias, clonospecific or patient specific probes are needed to detect MRD. Attempts to overcome these problems have relied on either specifically amplifying regions of the IgH gene which are commonly rearranged in B cell lymphoproliferative disorders[11] or by using 'consensus' or framework primers to amplify and sequence the complementary determining region of IgH.[12 13] The sensitivity of detection varies from one cell in 10^3 to one cell in 10^6 and can identify up to 95% of rearrangements. False positive and false negative reactions are found with all these techniques and also the inherent heterogeneity of leukaemic cells frequently results in an oligoclonal population of blasts showing multiple rearranged bands, not amenable to PCR analysis.[14]

T LINEAGE LEUKAEMIAS

Rearrangements of the gamma chain of the T cell receptor complex occur in most T lineage and a proportion of B lineage ALLs.[5 16] These rearrangements are much more restricted in their number of V regions and thus more amenable to PCR based analysis.[17] The delta chain of the T cell receptor complex rearranges before the gamma chain and a higher percentage of delta chain rearrangements have been documented in B lineage leukaemias.[18] Restricted numbers of gene rearrangements have meant that these can also be monitored using PCR based methods of 'remission' marrows, and one cell in 10^6 can be detected many months after diagnosis and frequently precedes clinical relapse.[19] Currently this would appear to offer the best PCR based method for assessing MRD, the only problem being the 20% of B lineage leukaemias with no detectable rearrangements of the TCR delta locus.

MOLECULAR CYTOGENETICS

Cloned translocation breakpoints will obviously provide the most sensitive and tumour specific MRD markers used in association with either DNA or RNA PCR methods. One example is the t(9;22) or Philadelphia translocation found in 98% of chronic myeloid leukaemias, and 20% of adult and up to 5% of childhood ALLs. Cytogenetically, the translocation appears identical in both diseases, but at the molecular level all chronic myeloid leukaemic breakpoints are within the breakpoint cluster region (bcr) gene on chromosome 22. The ALL breakpoints are more widely dispersed. After the t(9;22) translocation, the abl oncogene on chromosome 9 is translocated onto chromosome 22 adjacent to the bcr gene and fuses with it, resulting in a chimeric gene This produces a novel mRNA.[20] The entire coding region for the bcr gene has been cloned; and oligonucleotide primers, which detect both the normal and the abnormal bcr genes or the abnormal transcripts have been used with PCR technology in cells from patients with chronic myeloid leukaemia after allogeneic bone marrow transplantation or cells from patients with Ph' positive ALL in remission.[21 22] The value of screening cytogenetically negative blast cells for concealed aberrant bcr transcripts was recently demonstrated in a large series of both adult and childhood ALLs, of whom 55% and 6% respectively, were positive.[23]

Other recently cloned breakpoints such as the t(1;19) seen in pre-B ALL,[24] and t (14;18) seen in 85% of centroblastic/centrocytic lymphomas[25] and the retinoic acid receptor α gene rearrangements seen in the t(15;17) of promyelocytic acute myeloid leukaemia[26] have also proved amenable to PCR based MRD detection. In the case of the latter, it is likely that the beneficial pharmacological effect of retinoic acid is mediated via the α gene fusion protein. Hence the method can be used to suggest treatment options as well as monitor response to all-trans retinoic acid treatment with promyelocytic acute myeloid leukaemia.

Fluorescence in situ hybridisation and chromosome painting

Probably one of the most interesting recent techniques to assess MRD in leukaemias with chromosome abnormalities is fluorescence in situ hybridisation, using either DNA probes located at or near translocation breakpoints or chromosome painting using whole chromosome DNA.[27] The use of interphase cytogenetics involving non-mitotic cells lends itself to the analysis of remission bone marrow samples which contain few dividing cells. Centromeric probes which recognise specific repetitive sequences have been used to detect and quantitate their respective chromosomes in interphase nuclei.[28] In addition, probes which detect both numerical and structural cytogenetic abnormalities combined with morphological analysis of the relevant cells provide a rapid and accurate assessment of MRD.[29]

Conclusion

Unfortunately, in some cases the leukaemic clone may persist for many months or even years without overt relapse or any associated adverse clinical features. Thus, the significance of MRD and its ultimate relevance to treatment and long term survival will require both a large cohort of patients and detailed long term study using a variety of methods. The clinical relevance of MRD will only become important when both haematological and molecular criteria indicative of remission are achieved and sustained. This will then enable earlier cessation or alteration of treatment for a number of patients.

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I would like to thank my colleagues Drs J Chessells, F Cotter, I Hann, B Reeves, and D Goldblatt for critically reviewing the manuscript

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Stressful life events and childhood illness

An undesirable life event is defined as an adverse social experience with an identifiable onset, circumscribed course, and discernible end point, such as a death or permanent separation, the effects of which are likely to have an impact on an individual lasting more than a few hours. In other words, exposure to the adversity is relatively brief (hours or days) but the impact is substantive. Undesirable life events constitute a subclass of all types of life events (desirable, undesirable, and neutral) and one form of environmental experience that children are exposed to in everyday life. Ongoing difficulties are another form of social adversity, and refer to those social experiences where beginnings and endings are difficult to discern but indicate that a child is continuously being exposed to an undesirable experience, such as chronic marital disharmony, whose intensity and impact may wax and wane over time. For nearly 50 years life events and ongoing difficulties have been the subject of extensive research as potential causes of mental and physical disorders in individuals of all ages. It is only relatively recently, however, that different forms of life experiences to which children may be exposed have been the subject of classification and detailed research.[1]

Life events measurement

Questionnaires have been developed for parents and children to indicate the number of events that have occurred over a defined time period, often the previous 12 months. Events have invariably been weighted for likely stressful effects.[2 3] A grading of the 'stressfulness' of events such as parental death, divorce, personal illness, house or school move is then obtained. Unfortunately, there are considerable methodological problems with the measurement of life events by this procedure. Firstly, questionnaires invariably fail to cover all forms of recent life experiences; secondly, the wording of events is often ambiguous; thirdly, they cannot take into account the personal nature and qualities of events for children in different social and physical circumstances; and fourthly, they fail to determine when events occurred in relation to the onset or change (for example relapse or recovery) in the nature or course of disorder under investigation. To interpret the meaning of life events considerable effort should be expended in establishing the exact nature of the event and its temporal relationship with the episode (or change) of the illness.

Many of these methodological difficulties are overcome by using face to face interviews with parents and children.[4] Interview procedures provide a more sensitive method for determining the prevalence of events as well as collecting detailed personal information about the event (who was involved, its nature, salience to the individual, duration, and outcome). Such information allows a judgment to be made on the likely impact of an event on the child knowing its full nature and circumstances. This also takes into account the appreciable individual differences that occur in children's social circumstances even for so called identical events such as death of a parent. Ratings of the degree of undesirability of any event can be obtained from a number of sources including parents, child, interviewer, or another professional not involved in the collection of the life event data. In addition, the onset of events can be carefully noted and compared with the onset of disorder being investigated. These methodological and procedural advances have resulted in a much greater understanding of the causal role of recent undesirable life events in the onset and recovery of anxious and depressive disorders in school age children.[5–7]

Recent undesirable events and child psychiatric disorder

There is now considerable evidence to show that most children between the ages of eight and 16 experience between three and five life events per year. Desirable events appear to occur with equal frequency in psychiatric cases and controls.[8] There is, however, a significantly greater exposure to undesirable life events in the 12 months before the onset of psychiatric disorders in school age children compared with controls.[5] It is apparent, however, that undesirable events are neither necessary nor sufficient as causal factors in all cases of psychiatric disorder. Indeed, when they occur in isolation there are significant but modest increases in the risk, approximately fivefold, for the occurrence of anxious and depressive disorders. For the majority of childhood emotional disorders (perhaps 75%), however, undesirable events occur in combination with more ongoing difficulties such as distress and loneliness in mothers. Under these circumstances the risks of an episode of anxiety or depression are cumulative and may increase to as much as a hundredfold (as a consequence of multiplying together the known risks carried by each adverse experience) over children who are not exposed to this pattern of social adversities.[9] Cumulative effects are not however always as straight forward as they appear. For example an *absence of desirable events* in a child's life carries no increase in risk for anxiety or depression. If a child concurrently experiences friendship difficulties, however, then there is an appreciable increase in risk (tenfold or more) as a result of the interaction between the two circumstances.[8] In other words, no desirable events carries a latent enhancing effect which is activated only in the presence of a particular type of other social stressor. For example, no desirable events has no such latent effect in the presence of family focused life events. There are clearly a number of somewhat different psychological mechanisms that determine the effects of the environment on children's mental well being and development.[10 11] It has become apparent that we can no longer think of stress as an amorphous burden exerting rather non-specific mechanical effects on children's lives. Rather, we must begin to determine the specific associations between different patterns of social adversity and types of psychopathology at different ages and stages of development. It is also clear from numerous studies on children at risk that exposure to events and difficulties even in combination does not inevitable result in psychiatric disorder. In other words, some children show resilience in the face of social adversities.[10 12] Determining what constitutes resilience to undesirable life events is an important area for further research.

Stressful experiences and physical illness

As yet there are no reported studies using life event interview methods to investigate the role of stressful life events in the onset, maintenance, or relapse of physical illness in children. There has, however, been considerable research on children with physical disease using life event questionnaires. Thus diabetes, juvenile rheumatoid arthritis, Crohn's disease, ulcerative colitis, and haemophiliac bleeds are disorders in which an excess of stressful events have been noted, compared with controls.[13–15] In all of these studies no distinction was made as to whether or not events preceded the onset of symptoms or, more parsimoniously, the onset of an identified episode of the disease. It is unclear, therefore, if undesirable events precede the onset of episodes of these disorders, or that children with these disorders are more likely to experience undesirable life events.

One of the earliest and most seminal of studies on physical health in children was that of Meyer and Haggerty who followed up 100 children from 16 families prospectively over 12 months, undertaking throat cultures for streptococci every two weeks and having the family keep a diary of upsetting events that had occurred over the time period between throat cultures.[17] Approximately a quarter of streptococcal infections suffered by the children were preceded by upsetting events of varying kinds. The findings allowed the authors reasonably to conclude that, for a significant proportion of children, stressful life events were potential causal agents in the onset of their infections. Overall these research findings, together with much clinical experience, point to an important, but as yet undetermined role, for social adversities on the risk for relapse and recovery form physical illnesses. It remains much less clear if life events and difficulties contribute to the onset (that is the cause) of such illnesses.

What is currently needed are two different but complementary studies. Firstly, a prospective longitudinal study of a clinical population which systematically and concurrently documents the ebb and flow of physical illness, mood and behaviour, and changes in the environment. A study of this nature would provide repeated measures of life events and difficulties, and the physiological and behavioural state of the patient. Such a study would be able to determine the direction of effects between the environment and the child's physical and mental state. In addition, important information would be provided concerning which children were most likely to relapse as a consequence of environmental difficulties.

Secondly, an epidemiological longitudinal study in which well children at high risk for physical disease are screened and followed up until an illness develops. This would ensure the precise measurement of events, psychiatric status, and physical health before the onset of disease and determine their precedence to each other. Such approaches would provide much needed information on the role of environmental mechanisms and processes in the onset, maintenance, and outcome of physical diseases.

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ORIGINAL ARTICLES

The Scottish low birthweight study: I. Survival, growth, neuromotor and sensory impairment

The Scottish Low Birthweight Study Group[*]

Abstract

Of all 908 livebirths weighing less than 1750 g at birth who were born in Scotland in 1984, 896 (99%) were enrolled in a prospective study to document survival and determine the prevalence of neuromotor and sensory impairments and disability.

At the age of 4·5 years, 636 (71%) had survived and 611 (96%) were assessed. Overall 16% were disabled; 47 had cerebral palsy (52·5/1000 livebirths), seven were blind (7·8/1000 livebirths), and 11 were deaf and using aids (12·3/1000 livebirths). Among those not overtly disabled, the prevalence of poor neuromotor competence was high and related to birth weight.

All growth measures had mean values below the standard population mean indicating a downward shift in the distribution which was related to birth weight. In addition the height distribution was negatively skewed.

The improved survival of low birthweight infants documented in routinely collected vital statistics throughout the developed world has to some extent shifted the focus of concern from the risk of death to the quality of life of the children who now survive.[1] Over the years, reports from individual hospital units of the later outcome of very low birthweight (<1500 g) children have shown constant rates of disabling conditions that have ranged between 6% and 8%.[2] Follow up studies from specialist neonatal intensive care units, however, cannot provide true estimates of the risk of particular outcomes that can be compared with other populations because of the bias resulting from different referral practices. More precise estimates of the risk associated with being of low birth weight can be derived only from the examination of geographically defined populations.[3]

The aim of the current study was to document survival and the prevalence of neuromotor, sensory, and cognitive impairments in the geographically defined population of infants weighing less than 1750 g who were born in Scotland in 1984 and to relate these findings to the perinatal experiences, subsequent morbidity, and social circumstances of the children.

In this paper we present the data on growth and the prevalence of neuromotor and sensory impairments and disability.

Subjects and methods

Paediatricians providing neonatal care throughout Scotland collaborated in the early stages of the study. Information on all infants weighing less than 1750 g was provided from every maternity unit in the country and was cross checked with data collected routinely by the Information Statistics Division of the Common Services Agency, which is in turn linked to the Registrar General for Scotland's file on births and deaths. Perinatal data were collected retrospectively by one person (VF) by abstraction from obstetric and neonatal casenotes. Information on the children's status at 2 years was provided by hospital paediatricians, child health clinic doctors, and from health visitor interviews with the parents.[4]

A further assessment of growth and neurodevelopment and cognitive status at 4·5 years was carried out by 20 doctors working in the community child health services of each of the Scottish health boards; these doctors were unaware of the children's neonatal history apart from the fact that they had birth weight less than 1750 g. The doctors were brought together for discussion about the content of the assessment and standardised tests were demonstrated —in two instances by the authors of those tests. A six week pilot period was allowed followed by sessions to test and correct interobserver variation.

This paper is the first of a series and documents the prevalence of clinical outcomes in this population of children.

THE CONTENT OF THE ASSESSMENT

Height, weight, and head circumference were measured using equipment available in the clinics in which the children were seen and the results standardised for age and sex using reference charts.[5–7] Where children were assessed in the home, only height and head circumference were measured. A neurological assessment was carried out along the lines suggested by Amiel-Tison and Stewart,[8] and the child was given a brief clinical examination.

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Accepted 15 January 1992

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The Henderson revision of the Stott-Moyes-Henderson test of motor impairment (TOMI) was administered.[9] This test was originally designed to identify children whose motor competence fell into the lowest 15% of the general population. For the purposes of this study, and with the agreement of the author, we used the 10th centile as a measure of impaired performance. The recommended scoring of the test provides an overall score, but for the purposes of understanding more about the specific problems a child might have, agreement was reached with the test author that the items could be considered separately.

Details of the results of routine vision and hearing checks at school entry were requested from health boards.

DEFINITIONS

Impairment and disability were graded by the following criteria incorporating those set down in the World Health Organisation (WHO) classification of impairments, disabilities, and handicaps[10]:

Severe disability: those with neuromotor signs who were unable to sit, stand, or walk independently even with aids; who were blind or had acuity levels of less than 6/60 in the better eye; who were deaf or had a loss greater than 55 dB and were using aids; or who had an overall short form intelligence quotient (IQ) on the British ability scales of less than 50 (see accompanying paper).

Moderate disability: those with neuromotor signs who could sit, stand, and walk with aids, who had a corrected visual acuity of between 6/36 and 6/60 in both eyes, who had a hearing loss of 40-55 dB in the better ear even if hearing aids had not been prescribed; or who had an IQ in the range 50–69.

Impairment without disability: those who had neuromotor signs only without overt functional loss; those with a visual acuity of 6/18-6/24; or a hearing loss less than 40 dB; or who had an IQ between 70 and 84.

Overall disability was further divided into whether the child had single or multiple problems.

STATISTICAL ANALYSIS

Examination of the data did not detect any systematic variation between observers in the rate of abnormality detected except where it was explained by one doctor who saw all the study children who attended a special nursery for disabled children.

Analyses in this paper report on comparisons of the prevalence of the various outcomes in three birthweight groups (below 1000 g, between 1000 and 1499 g, and 1500–1749 g using χ^2 tests, χ^2 test for trend, and comparison of means using Student's *t* test.

The content of the assessment covers a wide variety of outcomes in the children, some of whom had specific disabilities in one sphere that affected their competence in tests of other skills—for example, a child who is blind is unable to perform a bead threading task. For this reason, and because some children refused some of the tests, the total numbers reported on each test vary. The issue of children who are unable to take part in testing because of disability is addressed in a future paper.

Results

In Scotland in 1984 there were 1044 registered births of children weighing less than 1750 g of whom 908 were born alive and eligible for inclusion in the study; 896 (98·8%) were enrolled. Twelve children were not enrolled because they were not reported to the study by medical records officers. They were identified over a year later through routine returns of the Scottish Morbidity Record (SMR2 and 11) data and were therefore not approached for consent.

SURVIVAL RATES

Of the 896 livebirths, 217 died before 28 days, an overall neonatal mortality rate of 242 per 1000 livebirths, with an appreciable difference between those with birth weights less than and greater than 1000 g in both singleton and multiple pregnancies (table 1). Female singleton births had higher survival rates than males but this sex difference in survival was not found for multiple births. Infants with birth weights of less than 1000 g had twice the rate of postneonatal death of the heavier infants. Among neonatal survivors, four times as many children weighing <1000 g died before the end of the first year.

Six children died between 1 and 2 years of age and a further child, who had been assessed at 2 years as multiply handicapped, died in an accident at the age of 4 years. In total, 71% of the children survived until assessment at 4·5 years.

Of the 636 survivors, 611 (96%) were assessed; 12 children had gone abroad, two had been adopted, and six parents refused to have their children assessed. Five children could not be traced after questioning the facilities of the Child Health Register, the National Health Service Register, and the local education authority.

The characteristics of the children and their families are shown in table 2. Although more boys were born in this birthweight group, their slightly higher mortality rates, particularly among those less than 1000 g, resulted in an approximately equal sex ratio among the survivors. Multiple pregnancies were more common in the lightest weight group. There was no differences between the birthweight groups in maternal age at delivery, the social class of the father, or being part of a single parent family at the time the child was assessed. The social class distribution of the study cohort did not differ

Table 1 The number of births and deaths of infants weighing less than 1750 g at birth, in Scotland in 1984: survival rates by birthweight group

	Birth weight			
	<1000 g	*1000–1499 g*	*1500–1749 g*	*Total*
No of livebirths	204	398	294	896
No of neonatal deaths (rate/1000 livebirths)	126 (618)	71 (178)	20 (68)	217 (242)
No of postneonatal deaths	14	13	9	36
Deaths 1–2 years	4	1	1	6
Deaths 2–4 years	0	0	1	1
No of survivors at 4·5 years (rate/1000 livebirths)	60 (29·4)	312 (78·4)	264 (89·8)	636 (710·1)
No assessed at 4·5 years (%)	60 (100·0)	298 (95·5)	253 (95·8)	611 (96·0)

significantly from that of the total Scottish birth population in 1984 when the high proportion of missing or incomplete social class data were excluded. All but five children were white.

Data from the SMR2[11] on births in the period 1980–6 were used to derive birth weight for gestation standards suitable for the study population (A Leyland *et al*, unpublished data).

Table 2 Characteristics of the children by birthweight group

	Birth weight			
	<1000 g	*1000–1499 g*	*1500–1749 g*	*Total*
Sex ratio at birth (M:F)	0·92	1·19	1·07	1·08
Sex ratio of survivors (M:F)	0·67	1·06	1·01	0·99
Birth number. % singleton at birth	72·1	78·4	83·0	78·5†
Mean maternal age at delivery (years)	25·2	25·6	25·5	25·5
Social class of father at 4 years (%).				
I and II	18·3	14·4	19·0	16·7
III non-manual	8·3	5·7	5·5	5·9
III manual	23·3	35·6	30·4	32·2
IV and V	20·0	19·1	18·2	18·8
Other+missing	30·0	25·2	26·9	26·4
Single parent at 4 years (%)	15·0	11·1	13·8	12·6
Small for dates (% <10th centile).				
At birth	22·4	30·4	38·1	31·4†
Survivors	34·8	35·5	38·0	36·5
Mean (SD) age at assessment (months)	55·3 (2·2)	55·5 (2·6)	55·6 (2·9)	55·5 (2·7)

*Singleton births only.
†χ^2 for trend=p<0·005.

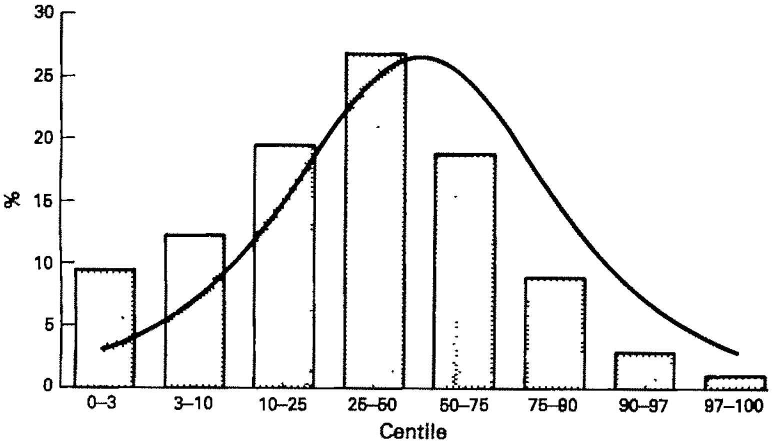

Figure 1 Distribution of height at 4·5 years of all children <1750 g at birth, 1984. Based on 601 children; 10 missing cases.

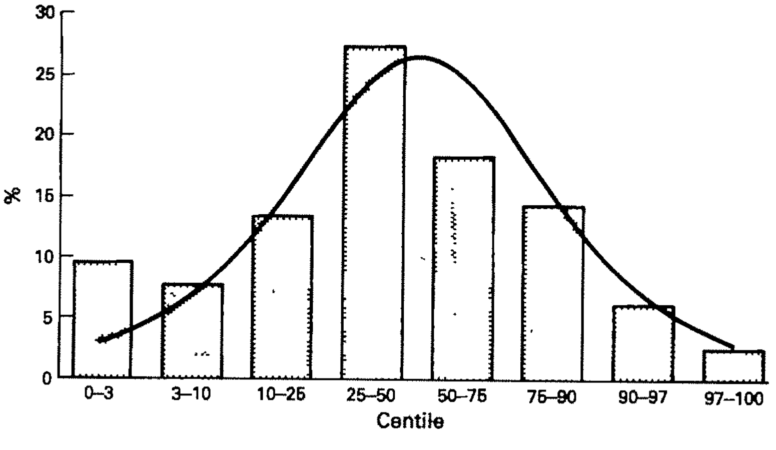

Figure 2 Distribution of head circumference at 4·5 years of all children <1750 g at birth, 1984. Based on 603 children; eight missing cases

Because our study population was defined by birth weight alone, significantly more of the population with birth weights greater than 1000 g were below the 10th centile of weight for gestation for this population; among survivors, however, a higher proportion of the less than 1000 g infants were small for dates.

The mean age at assessment was 55·5 months, with no difference between the birthweight groups.

GROWTH

Figures 1–3 show the distribution of height, head circumference, and weight centiles in the study cohort calculated from standard centile charts using chronological age.[5 6] All the growth measures had mean values below the standard population mean, indicating a downward shift in the distribution. This shift was related to the original birth weight. It was only in respect of later weight that children with birth weights less than 1000 g differed from the rest of the cohort; 90% of this group had weights less than the 50th centile at 4·5 years.

In addition, the height distribution was negatively skewed (skewness −0·67, SE 0·13). Boys' height was more affected than girls with the result that there was a sex difference in body mass index (weight/height^2). Figure 4 shows that there was excess of children with body mass index below the 50th centile—that is, they were light for their height.

The heights and weights of children who were originally small for dates did not differ significantly from those of the other study children, but a statistically significantly higher proportion of them had head circumferences less than the 10th centile (p<0·005).

NEUROMOTOR IMPAIRMENT

The observed birthweight gradient in the proportion of surviving children who had neuromotor impairment with disability was statistically significant but no gradient was seen in the rate per 1000 livebirths (table 3). Thirty five children (5·7%) had clinical signs only, most commonly restricted dorsiflexion of the ankles or tight hamstrings which were not sufficiently severe to stop them functioning, albeit clumsily.

SENSORY IMPAIRMENT

Sensory impairment was commoner in children with birth weights less than 1000 g. Seven children were blind and 70 had squints frequently associated with a more general neuromotor impairment. Twelve children overall had nystagmus denoting a central lesion.

Information on refractive errors was not available for all the children in three health boards, partly because children moved schools. For children who were living in England we were not in a position to obtain this information. Records were available for 478 children of whom 22 (3·5%), in addition to those who were blind, had a visual acuity level of 6/18 or less in both eyes. This finding was related to birth weight, with 9% of those with birth weights

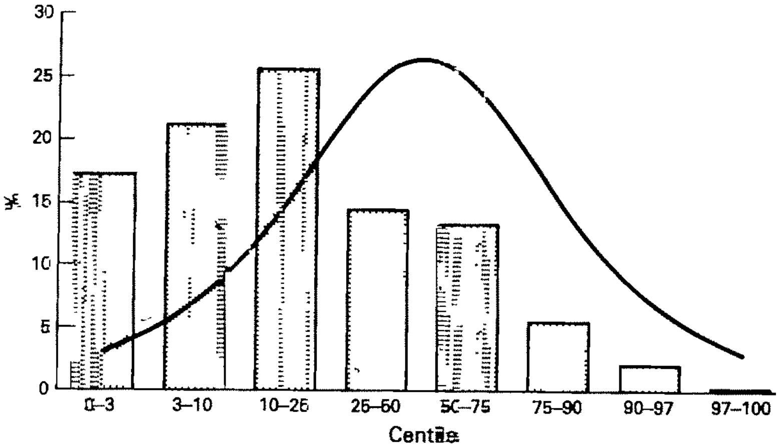

Figure 3 Distribution of weight at 4·5 years of all children <1750 g at birth, 1984. Based on 551 children; 60 missing cases.

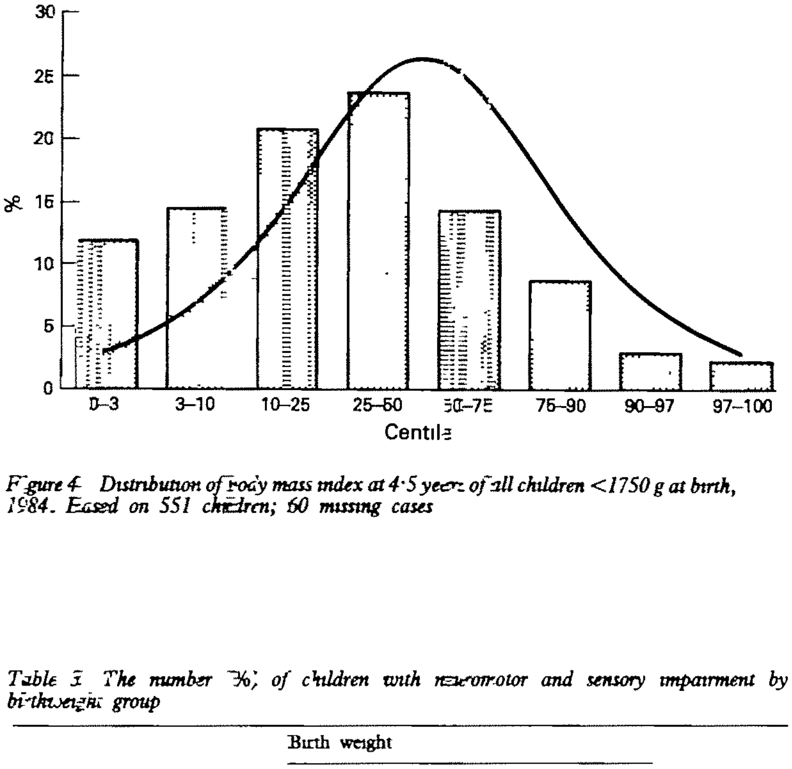

Figure 4 Distribution of body mass index at 4·5 years of all children <1750 g at birth, 1984. Based on 551 children; 60 missing cases

Table 3 The number (%) of children with neuromotor and sensory impairment by birthweight group

	Birth weight			
	<1000 g	1000–1499 g	1500–1749 g	Total
No of children assessed	60	298	253	611
Neuromotor impairment	13 (21·6)	42 (14·1)	27 (10·7)	82 (13·4)†
Abnormal signs only	5 (8·3)	16 (5·4)	14 (5·5)	35 (5·7)
Impairment with disability:				
Severe	4 (6·7)	10 (3·4)	9 (3·6)	23 (3·8) } ‡
Moderate	4 (6·7)	16 (5·4)	4 (1·6)	24 (3·9) }
Rate of neuromotor disability/1000 livebirths	39·2	65·3	44·2	52·5
95% CI	17·1 to 75·8	43·1 to 94·3	23·8 to 74·4	37·9 to 67·1
Visual impairment				
Blind	3 (5·0)	1 (0·3)	3 (1·2)	7 (1·1)
Squint	12 (20·0)	35 (11·8)	23 (9·2)	70 (11·6)
Nystagmus	5 (8·8)	2 (0·7)	5 (2·0)	12 (2·0)
Visual acuity <6/18	5 (9·4)	10 (4·4)	7 (3·6)	22 (4·6)
Rate of blindness/1000 livebirths	14·7*	2·3	10·2	7·8
95% CI	3·0 to 42·4	0·3 to 13·9	2·1 to 29·6	3·1 to 16·0
Hearing impairment:				
Deaf with aids	2 (3·0)	4 (1·4)	5 (2·0)	11 (1·8)
Hearing loss >40 dB	0	2 (0·6)	2 (0·7)	4 (0·6)
Rate of deafness/1000 livebirths	9·8	10·3	17·1	12·3
95% CI	1·2 to 34·9	2·7 to 25·5	5·6 to 39·4	4·6 to 17·5

CI=confidence intervals
χ^2: *$p<0·01$; χ^2 for trend †$p<0·05$, ‡$p<0·025$

below 1000 g being affected, compared with 4% of those over 1000 g at birth.

Eleven children (2% of those for whom results were available) were deaf and using hearing aids and a further four had bilateral losses of 40 dB or more; infants who had been less than 1000 g at birth did not have an increased risk of deafness. Information on the results of school entry screening was available for 526 (86%) of the children. In the case of 19 children (3·6%), where the 'sweep' test had been reported as abnormal, the results of audiometry were not available.

MOTOR COMPETENCE

The results of the TOMI for children without a known neuromotor or visual disability are presented in table 4. On the overall score the children performed significantly less well than the population on whom the test was standardised, even in the absence of neuromotor disability with 40% of those below 1000 g being considered impaired compared with 20% and 16% in the heavier groups respectively. This trend was, however, statistically significant only in respect of performance of the tasks of bead threading, one leg balance, and jumping the cord. Where there was no trend by birth weight, the extremely low birthweight infants (<1000 g) performed less well on catching a bean bag and rolling a ball into a goal. Nearly a fifth of all the study children could not jump a cord at knee height but in children who had birth weights less than 1000 g, 36% failed this task, whereas 90% of the reference population on whom the test was standardised could achieve it.

In tests of fine motor skills the study children were poor at, for example, controlling a pencil to draw between two lines (the bicycle trail task), with nearly a quarter of those over 1000 g and 30% of the extremely low birthweight children scoring below the 10th centile for the tests.

DISABILITY STATUS

Children were classed into four categories: (i) ***severely disabled*** with single or multiple systems involved; (ii) ***moderately disabled*** with single or multiple systems involved; (iii) ***impaired but not disabled;*** and (iv) as having ***no detectable impairment.*** These overall categories took neuromotor and sensory status into account, and the level of cognitive impairments described in the accompanying paper. Using the criteria described earlier in the paper, 36 of the whole cohort (5·9%), were severely disabled; in those children weighing less than 1000 g, this proportion was 13%, and in the higher birthweight groups, it was 5% (table 5). More than half (55%) of the cohort were free of obvious impairment, ranging from 42 to 58% between the lowest and the highest birthweight groups. Multiple disabilities were twice as common in the <1000 g group as in the heavier children.

Discussion

Longer term follow up of low birthweight children is expensive and is logistically difficult

Table 4 Motor competence in children with no known neuromotor or visual disability: number (%) children <10th centile for individual tests by birthweight group

	Birth weight			
	<1000 g	*1000–1499 g*	*1500–1749 g*	*Total*
Rolling ball into goal	11 (23·4)*	26 (10·1)	26 (10·9)	63 (11·6)
Catching beanbag	12 (25·5)*	30 (11·6)	29 (12·2)	71 (13·1)
Threading beads	14 (29·7)	53 (20·5)	32 (13·4)	99 (18·2)†
Posting coins	13 (28·9)	46 (18·0)	37 (15·7)	96 (17·9)
Bicycle trail	15 (31·9)	54 (21·0)	52 (21·8)	121 (22·3)
Jumping cord	17 (36·2)	58 (22·5)	38 (15·9)	113 (20·8)‡
Walking heels raised	12 (25·5)	37 (14·3)	31 (13·0)	80 (14·7)
One leg balance	16 (34·0)	50 (19·5)	40 (16·8)	106 (19·6)†
Overall score§	18 (40·0)	51 (20·2)	39 (16·5)	108 (20·3)‡

*χ^2=p<0·05; χ^2 for trend: †p<0·005
§Overall score for those who did all tasks

Table 5 Overall disability rating of children: number (%) by birthweight group

	Birth weight			
	<1000 g	*1000–1499 g*	*1500–1749 g*	*Total*
No of survivors	60	298	253	611
Unimpaired at 4·5 years	25 (41·7) } *	162 (54·4)	147 (58·1)	334 (54·7) } †
Impaired but not disabled	15 (25·0)	90 (30·2)	69 (27·3)	174 (28·5)
Moderate disability:				
Single system	10 (16·7)	22 (7·4)	18 (7·1)	50 (8·2)
Multiple systems	2 (3·3)	10 (3·4)	5 (2·0)	17 (2·8)
Severe disability				
Single system	3 (5·0) } *	7 (2·3)	6 (2·4)	16 (2·6)
Multiple systems	5 (8·3)	7 (2·3)	8 (3·2)	20 (3·3)

χ^2 *p<0·05, χ^2 for trend †p<0·05.

because of the problem of tracing children but more studies of children who were of low birth weight and who are now reaching or have just reached school age are now being reported. The majority are, however, based on the survivors of neonatal care in a single intensive care setting.[12–14] Where geographically based studies are available, the population described is usually enrolled over a period of several years, during which time elements of the perinatal care they received may have subtly changed[15–17]; some have reported only at earlier ages.[18] Sometimes these studies have reported on children covering a wide age range of subjects at the time of assessment with the consequence that the same methods of assessment were not appropriate for the whole study population.[15]

Many studies have reported on the poorer growth of low birthweight infants.[19–24] In our cohort, the distributions of all measures of growth were shifted downwards with the most marked effect being for weight; a similar pattern was reported by Casey *et al.*[25] A quarter of the children with heights below the 3rd centile had severe cerebral palsy and this finding was independent of social class and mean parental heights. The head circumference of children with cerebral palsy formed a U shaped distribution with just over 30% being above the 97 centile.[26]

In all published studies, the prevalence of neuromotor and sensory impairment is related to the original birth weight with the smallest infants having the highest rate of impairment. This finding is borne out by our study. In the report of Kitchen *et al* (1982) over 13 years of the outcome for infants of less than 1500 g from Melbourne, the proportion of surviving children with cerebral palsy rose in three time periods, the rates for 1966–70, 1973–4, and 1977–8 being 2·6, 4·5, and 11·9% respectively. Survival rates were 37% in the first two cohorts and 68% in the third.[27] In Scotland, survival rates in 1984, six years later, were 62% for children weighing less than 1500 g at birth with a cerebral palsy rate of 9·8% among the survivors. In a more recent report of infants who weighed less than 1000 g, born in the same tertiary centre in Melbourne between 1978–80,[28] 8·3% (five of 60 survivors) had cerebral palsy compared with 13·3% (eight of 60) in our study.

In these authors' *regional* study of 1979–80 births under 1000 g, however, the prevalence of cerebral palsy was identical to ours at 13·5%.[29] This highlights the importance of comparing geographically defined and thus similar populations.[30]

Johnson and her colleagues (1987), in a population based cohort study in Newfoundland,[31] reported similar survival rates for infants <1500 g born in 1980–1; 10% of the survivors had significant disability (including cerebral palsy) at 3 years whereas 6% of our <1500 g cohort had severe disability. Some of this difference may result from definitions of disability grades, but also, because our children were older, we were able to include measures of cognitive ability in the overall categorisation of disability.

When a prospective cohort approach has been employed it has been suggested that neurodevelopmental assessments at 1 year are predictive of neuromotor status at four years.[32] On the other hand, studies of the prevalence of cerebral palsy in populations suggest that reports at 3 years are likely to underestimate the numbers of children with moderate disability.[33] In this study there was 89% concurrence in the assignment of neuromotor status among those children seen at both 2 and 4·5 years; most of the newly diagnosed cases were of a milder nature.

Comparisons of disability rates between populations are difficult because even where the overall assessment is based on strict criteria covering individual aspects of development, it is the interaction between these spheres which influences how the child performs in everyday life. A child who has a moderate hearing loss alone cannot be classed along with a child who has perhaps slightly less severe impairments in vision, hearing, and in intellectual capacity. It is in this context that a subjective element contributes to the grading disability. Nevertheless without an overall measure of functional disability it is impossible to summarise the impact of increasing survival rates on long term outcome.

Saigal *et al* (1989) showed a decreased rate of disability in 3 year old infants with birth weights between 801 and 1000 g in a comparison of births between 1977–80 and 1981–4, but no difference in impairment without disability or survival rates.[34] Few of these extremely low birthweight infants seem to have had multiple impairments. In our study of slightly older children where cognitive assessment was included in the judgment of disability status, 33% of those less than 1000 g were moderately or severely disabled and 12% had mulitple systems affected.

The only similar study covering a nationwide population born in one year and seen at 4·5–5 years is the Netherlands study covering 94% of livebirths of children in 1983 who either weighed less than 1500 g or who were born at less than 32 weeks.[35] They also achieved a follow up rate of 96%. They report their findings in terms of WHO classification of impairments, disabilities, and handicaps.

It must be remembered that this is a classification system; it does not provide definitions of the level of involvement which constitutes a disability except for levels of hearing and vision loss which are specified. This makes direct comparison of the studies difficult. Furthermore, we have deliberately avoided the term 'handicap' as by definition, that requires 'a value to be attached to an individual's situation and experience when it departs from the norm' . . . 'It is regarded as a classification of circumstances in which disabled people are likely to find themselves'.[10] We did not feel our data allowed us to make such assumptions until the children were of an age when they could contribute their own perceptions of their disability and how it affected them 'relative to their peers'. It seemed appropriate therefore to combine the categories of disability and handicap from the Netherlands study for comparison with our findings (table 6).

A higher proportion of the Scottish children died before the age of assessment but this difference was not statistically significant (χ^2=3·36, df1, p>0·05). The proportion who were disabled/handicapped in the Dutch study was 28·5% compared with 17·6% in this study (χ^2=15·2, df1, p<0·001). The differences between the studies in the proportion who were normal and impaired was so great that they must be due to definitional differences.

Our 'normal' children were defined as having an IQ of 85 or over, no neurological signs, visual acuity of 6/12 or better, and no detectable hearing loss on clinical grounds. Some were perhaps clumsy Given these caveats, a comparison of the findings for those below 1500 g is shown in table 6.

One possible explanation is that in the Dutch study a screening test (the Denver developmental screening test) was used whereas in the Scottish study, a diagnostic psychometric test was administered. The former by definition will have false positives.

In addition, they had access to audiometry on all the children which may have identified more cases with hearing loss which did not interfere with functional performance. Comparisons on neuromotor function cannot be made since the motor developmental assessment used is not specified, nor the cut off point used to define impairment. The neurological assessment carried out was, however, designed to be very similar (P Verloove-Vanhorick, personal communication).

Nevertheless, the definition of disability is the same in both studies. It is unlikely that children who were considered clumsy by the TOMI would have been considered disabled in the Dutch population.

A more optimistic perspective from our study is that 62% of liveborn infants weighing less than 1500 g in 1984 survived to 4·5 years and that 60% of these were considered normal on the basis of the assessments carried out. Among those with birth weight between 1500 and 1749 g, 89% survived and 64% of the survivors were judged to be normal. Although survival rate is much higher in the heavier weight group, the proportion thought to be normal is not dissimilar.

Together with children with minor impairments, like squints, refractive errors or IQs between 70–84, 82% of the survivors who had weighed less than 1500 g and 85% of the heavier group were expecting to attend normal schools; in addition, some of the moderately disabled children will be integrated into normal schools.

These findings and those in the accompanying paper suggest that a substantial proportion of these children will continue to require support from the health and educational services well into the future.

Table 6 Comparison of findings on children with birth weights less than 1500 g with those of 1983 Netherlands study[17]

	Netherlands study	*Scottish study*
No of livebirths	1097	603
Dead	330	197
No (%) eligible for assessment	767 (69·9)	373 (61 8)
No (%) assessed	736 (96·0)	358 (96 0)
'Normal'	156 (21 2)	187 (52 2)
Impaired	370 (50 3)	105 (29·3)
'Disabled' or 'handicapped'	210 (28 5)	66 (18 4)*

*χ^2=13 0 df1 p<0 001.

We are grateful to the chief administrative medical officers in each health board for funding the time and travel of the community child health doctors participating in the study; to Tom Lynch for administration of the field work, and to Gaye Bell for patiently coping with the redrafting process We acknowledge with gratitude the helpful comments of colleagues within the unit

Most of all we would like to thank the children and their parents who gave up their time to the study.

The personnel involved in the planning, administration, and analysis of the project, Lesley Mutch, Anna McGee, Tom Lynch, and Gaye Bell, were supported by the Medical Research Council

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Archives of Disease in Childhood 1992; 67: 682–686

The Scottish low birthweight study: II. Language attainment, cognitive status, and behavioural problems

The Scottish Low Birthweight Study Group*

Abstract

Of the 636 survivors of a total geographically based population born in Scotland in 1984, who weighed less than 1750 g at birth, 611 (96%) were assessed at 4·5 years to determine the prevalence of language, cognitive, and behavioural problems.

Language development was significantly related to birth weight, gestational age, and social class for comprehension, less so for expressive language.

Mean (SD) intelligence quotient (IQ) on the British ability scales was 92·9 (14·7). Within this population there were no signficant differences between birthweight groups. Overall they performed poorly on visual recognition, verbal comprehension and number skills subscales—in the latter those with birth weights <1000 g were significantly worse than the heavier children. Only 5% had IQs <70, but a further 3% could not be tested because of other physical disability. Among those with normal IQs were groups of children who exhibited patterns of skill deficits in different subscales raising the possibility of specific learning difficulties.

Poor attention span was reported in 47%, and parents said the study children had more behavioural problems than their siblings.

Many studies have reported the prevalence of disorders of language, cognitive impairments, and behavioural problems in selected populations of low birthweight children.[1-6] Fewer have described these outcomes in geographically defined populations.[7-11] Comparisons of the prevalence of these outcomes are confounded by several factors which include low follow up rates, different ages at assessment and therefore the need for different test procedures that may not be comparable,[12] and different exclusion criteria so that children with disabilities in other domains may not be included. In this study we have attempted to address these problems to provide a more complete picture of the performance of children with low birth weights just before they enter school.

Methods

The methodology of the study is described in detail in the accompanying paper.[13] Of 908 liveborn infants born in Scotland in 1984 who weighed less than 1750 g, 896 (99%) were included in the study. There were 636 survivors (71% of the original cohort); 611 (96%) were assessed at 4·5 years.

Twenty selected clinical medical officers from all the health boards in Scotland were brought together for discussion and demonstration of the techniques to be employed in the assessment of the children. A six week pilot period was allowed for them to familiarise themselves with the tests and was followed by sessions to assess interobserver reliability. Where necessary, verbal and written instruction on the administration of the tests was given in an attempt to maintain comparability between examiners.

CONTENT OF THE ASSESSMENT

Language competence was assessed using the Renfrew action picture test (APT) and the bus story test of continuous speech (BSTCS).[14 15] At 4 years these tests have been shown to be the most highly predictive of persistent language problems.[16] In the APT a standard sentence is used to ask the child to give a description of what is happening in a picture. It is scored, first, on the number of accurate items of information given, and second, on the grammatical correctness of the response. The BSTCS consists of a short story with pictures which is read to the child who is then asked to repeat the story while looking at the pictures. Some aspects of the story can be told by looking at the pictures but an additional component relies on auditory recall of the story as told. The number of items of correct information are scored and the average length of sentence produced is noted. The tests were tape recorded and the tapes were scored by the test author (CR) who had no other information about the child.

Parents were asked to comment on their perception of the child's maturity in respect of understanding and speech and to categorise him or her as being at, above or below the child's chronological age.

Cognitive ability was assessed using the British ability scales (BAS) covering verbal comprehension, visual recognition, naming vocabulary and recall of digits (which allowed the calculation of a short form intelligence quotient (IQ)) and

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Accepted 15 January 1992

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basic number skills.[17] The BAS were standardised on a sample of British children in 1973. In order to provide more recent Scottish norms, a sample of 100 Scottish children were assessed; these children were aged between 54 and 57 months, and were attending nurseries in Edinburgh and Glasgow. The mean (SD) IQ of this group was 99 (13·4) which is close to the test norms of 100 (15).

Parents completed the modified Rutter behavioural questionnaire for the index child and for a sibling where there was one of an appropriate age.[18] As part of the test of motor impairment,[19] the examiners completed a questionnaire which described the child's ability to cope with the test situation.

ANALYSIS

All test results were examined to ensure that there were no statistically significant differences between the examiners in the proportion of children who refused or failed the individual tests. In one component of the BAS, one examiner had significantly more children who refused or were reported as unable to do the test of number skills. This group of children did not differ from the rest of the cohort in either their social class distribution or nursery school attendance. In none of the other tests carried out was this examiner different from the others. Data on all the number skills tests administered by this examiner were therefore excluded from the analysis.

Some children had scores on the subscales of the BAS which indicated a level of ability level below the first centile for the child's age. A total of 24 children scored less than the first centile for their age on at least one of the subscales. This meant the child could not be allocated a T score for that scale. The T scores of these subscales are used to calculate the overall IQ. It would have been wrong to omit these children from the analysis as they attempted the tests but were unsuccessful; excluding them would have artificially raised the mean scores. In order to overcome this anomaly of the test construction these children were given an arbitrary T score of 26–that is, one point less than the lowest score the test recognises. As a consequence, the mean IQ derived from these four scales may be over estimated. On the other hand, in the verbal comprehension subscale a child of 4·5 years with all the answers correct, cannot achieve more than a T score of 59 which represents the 81st centile, thus underestimating his or her performance.

Table 1 Number (%) of children with scores <25th and >75th centiles on language attainment scales by birthweight group

	<1000 g	*1000–1499 g*	*1500–1749 g*	*Total*
Action picture test				
No of children tested	49	277	232	558
Information score				
<25th centile	14 (28·5)	47 (17·0)	42 (18·1)	103 (18·5)*
>75th centile	11 (22·4)	50 (18·1)	65 (28·0)	126 (22·6)
Grammar score:				
<25th centile	14 (28·5)	80 (28·9)	63 (27·2)	157 (28·1)
>75th centile	6 (12·2)	26 (9·4)	48 (20·7)	80 (14·3)**
Bus story test of continuous speech				
No of children tested	40	249	203	492
Information score:				
<25th centile	23 (62·5)	128 (51·4)	80 (39·4)	233 (47·4)**
>75th centile	9 (22·5)	38 (15·3)	49 (24·1)	96 (19·5)
Sentence length				
<25th centile	18 (45·0)	109 (43·7)	70 (34·5)	197 (40·0)
>75th centile	7 (17·9)	31 (12·4)	40 (19·7)	78 (15·9)

*p<0·02 <1000 g *v* rest, **p 0·005 <1000 g *v* rest.

Comparisons between groups and the strength of associations were tested using the χ^2 test and χ^2 for trend, where appropriate; comparisons of means were tested by Student's *t* test. Paired *t* tests were used for comparison between index children and their siblings.

Results

Twenty children (3%) could not be tested using the standardised assessments because of severe disability, either blindness, severe cerebral palsy, multiple congenital defects or, in one case, autism. These children were assessed using modifications of the tests which took account of their remaining skills and this will be reported separately. Technical problems with tape recorders in the language tests means that the number of children whose results were dependent on the tapes to be available for scoring, was less than the total assessed on other fields.

LANGUAGE ATTAINMENT

The number and proportion of children with scores below the 25th and above 75th centile for the Renfrew tests in each birthweight group are shown in table 1. The study population as a whole differed from the test standards for the information score in the APT with fewer than expected performing <25th centile and fewer >75th centile (p<0·001). Significantly more of the extremely low birthweight infants scored below the 25th centile of the test than those with higher birth weights (p<0·02). In the grammar score of this test, twice as many of the children with birth weights over 1500 g, compared with those below, scored above the 75th centile (p<0·005).

In the BSTCS, which involves auditory memory as well as visual recognition and expression, 47% of the whole study population scored less than the 25th centile in respect of information retrieval; the group with birth weights less than 1000 g performed less well than those over 1500 g (p<0·005). There was little difference between the birthweight groups in the length of sentence produced.

The information score of the APT was significantly associated with birth weight (p<0·05), gestational age (p<0·005), and the social class of the father (<0·0005), but was not affected by the mother's educational qualifications. In the BSTCS the information score, which involved, in addition, auditory recall, there was a significant association only with father's social class (p<0·05). The grammar score of the APT was significantly associated with birth weight (p<0·02), gestational age (p<0·05), social class (p<0·005), and mother's

Table 2 The distribution of psychometric scores (IQ) on the British ability scales: number (%) of children by birthweight group

	<1000 g	*1000–1499 g*	*1500 g+*	*Total*
No of children assessed	60	297	254	611
British ability scales				
Mean IQ (SD)	91 9 (15·3)	92 3 (15 2)	93·8	92 9 (14 7)
<70	4 (6 7)	15 (5 1)	(14 0)	30 (5 3)
70–84	12 (20 0)	73 (24·6)	11 (4 3)	137 (24 1)
85–115	34 (56·7)	174 (58·6)	52 (20 5)	367 (64 5)
115–	2 (3·3)	21 (7 1)	159 (62 6)	35 (5 7)
Not scored because of			12 (4 7)	
disability	7 (11 7)	6 (2 0)		22 (3 6)
Refused some of the tests	1 (1 7)	9 (3 0)	9 (3 5)	20 (3 3)
			10 (3 9)	

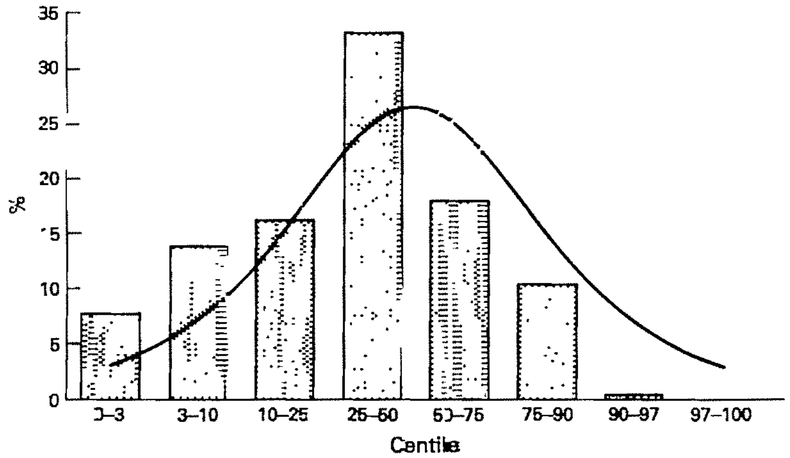

Figure 1 Distribution of verbal comprehension at 4 5 years of all children <1750 g at birth, 1984. Based on 591 children; 20 missing cases.

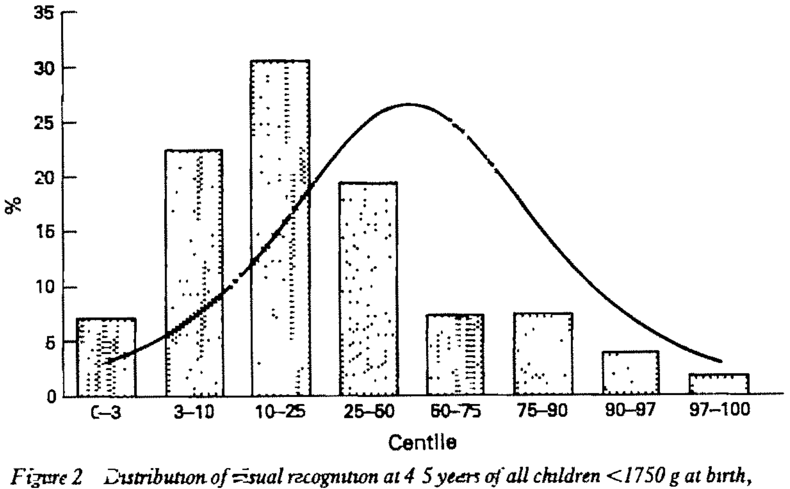

Figure 2 Distribution of visual recognition at 4 5 years of all children <1750 g at birth, 1984. Based on 589 children, 22 missing cases.

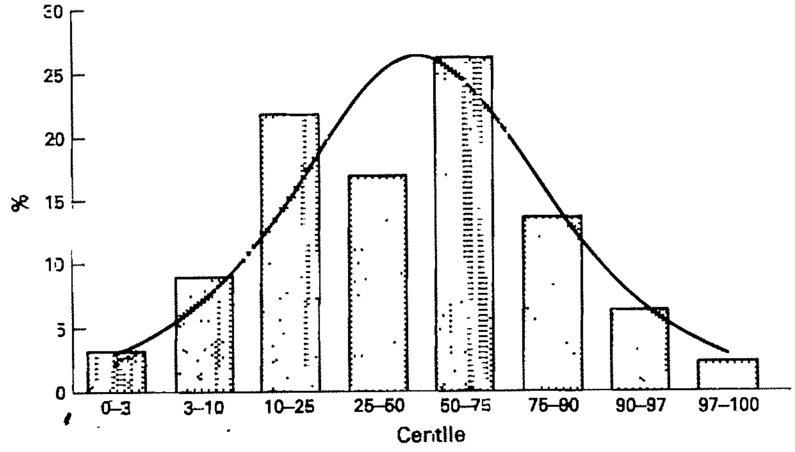

Figure 3 Distribution of naming vocabulary at 4 5 years of all children <1750 g at birth, 1984. Based on 589 children 22 missing cases

educational qualifications (p<0·05). There was no relationship between birth weight or gestational age and the length of sentence used by the child in the BSTCS, but again father's social class (p<0·005) and, in this case, the mother's educational qualifications significantly affected the score (p<0·05).

An articulation defect was identified in 20% of the children; this finding was not birthweight related. Although this was sometimes an isolated finding, it was more commonly present in association with other evidence of neuromotor disability. Its presence was regarded by parents as evidence of immaturity. Parents' perceptions of their child's maturity with regard to comprehension and expression correlated well with scores on the verbal comprehension (p<0·005) and naming vocabulary (p<0·005) subscales of the BAS.

COGNITIVE STATUS

The mean IQ for the whole group was 92·9 (SD 14·7, SE 0·6) which was lower than the test norm of 100 (SD 15, SE 4·1); this difference is not statistically significant. There were, however, no differences between the mean IQs of the birthweight subgroups (table 2). Five per cent of the study children had IQ scores under 70 indicating moderate mental retardation, but 71% of the children scored 85 or more, indicating average or above average cognitive development.

The distribution of the scores on the subscales of the BAS is shown (fig 1-5) and the numbers of children assessed on each of the subscales together with their mean scores (SE) is shown in table 3. The mean scores for verbal comprehension, visual recognition, and number skill scales were significantly lower than the test standards.

The study population did not differ from the test standards in the proportion of children with scores less than the 10th centile for the subscales of naming vocabulary in the digit recall (testing short term memory) (table 4). A significantly higher proportion of the total study population scored below the 10th centile on the visual recognition scale (which tests both short term memory and visuoperceptual skills), and on the verbal comprehension and number skills scales (p<0·001). Statistically significant differences relating to birth weight were found in the number skills component of the test (p<0·05) (table 4).

There was good agreement between the verbal comprehension score on the BAS and the information scores on the Renfrew tests (p<0·0001).

BEHAVIOUR

Significant behavioural problems, denoted by a score of 11 or more on the modified Rutter questionnaire, were present in 15% of the cohort with no significant differences between the birthweight groups; nor was there a significant effect of birth weight on the mean score of the total Rutter score or its component parts, the neurotic and conduct scores (table 5). Both of these latter scores were unaffected by sex, but

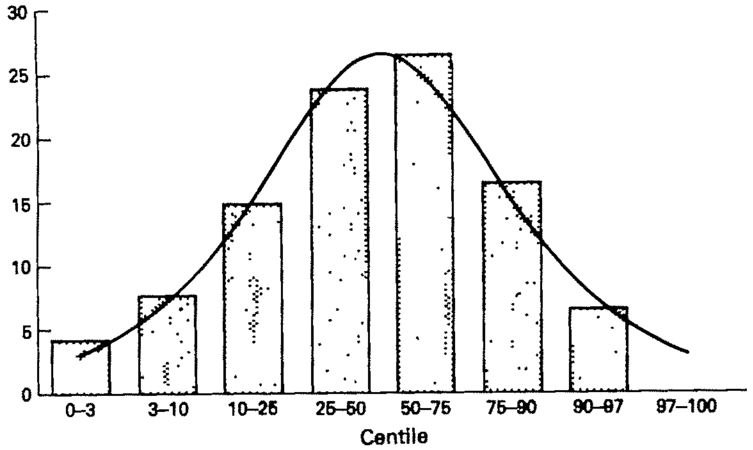

Figure 4 Distribution of digit recall at 4·5 years of all children <1750 g at birth, 1984 Based on 571 children; 40 missing cases.

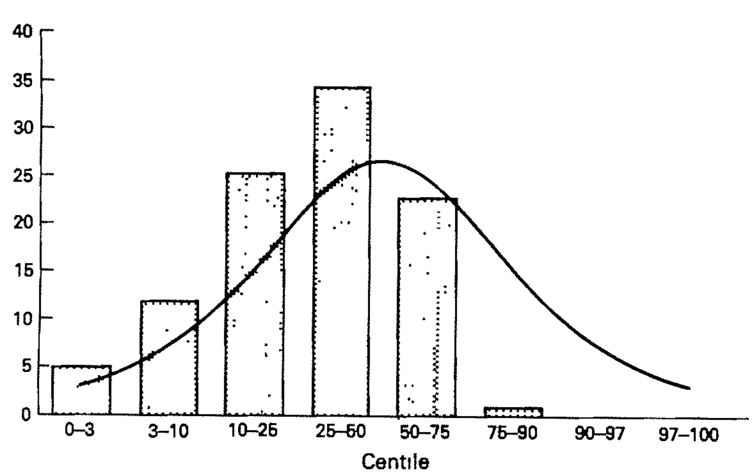

Figure 5 Distribution of number skills at 4·5 years of all children <1750 g at birth, 1984. Based on 538 children; 73 missing cases

Table 3 The number of children assessed on each of the subscales, mean and 95% confidence intervals (CI), and the number scoring below the 1st centile

	No of children	*Mean (95% CI)*	*No <1st centile*
Verbal comprehension	591	45·0 (44·3 to 45·7)*	8
Visual recognition	589	43·2 (42·4 to 44·0)*	13
Naming vocabulary	589	48·9 (48·1 to 49·7)	2
Digit recall	571	49·1 (48·3 to 49·9)	13
Basic number skills	538	44·2 (43·6 to 44·8)*	12

*p<0·05 significantly lower than test standards.

Table 4 Numbers (%) children scoring <10th centile on subscales of British ability scales: by birthweight group

	<1000 g	*1000–1499 g*	*1500 g+*	*Total*
Verbal comprehension	15 (27·8)	66 (22·7)	47 (19·1)	128 (21·7)
Visual recognition	12 (22·6)	96 (26·8)	66 (26·8)	174 (29·5)
Naming vocabulary	6 (11·3)	33 (11·4)	33 (13·4)	72 (12·2)
Digit recall	6 (11·3)	39 (13·8)	23 (9·8)	68 (11·9)
Basic number skills	12 (24·0)	49 (18·4)	30 (13·5)	91 (16·9)+

+χ^2 for trend, p<0·05

Table 5 Mean scores (SD) on Rutter parental questionnaire for study children by birthweight group and for siblings

	<1000 g	*1000–1499 g*	*1500–1749 g*	*All <1750 g*	*Siblings*
Total score	6·3 (4·3)	6·6 (4·4)	6·5 (4·3)	6·5 (4·3)	5·6* (4·4)
Conduct score	4·7 (3·4)	4·7 (3·5)	4·5 (3·5)	4·6 (3·5)	3·7** (3·4)
Neurotic score	1·6 (1·9)	1·8 (1·9)	2·0 (1·9)	1·8 (1·9)	1·9 (2·0)
No (%) scoring >11	13 (22·0)	58 (20·3)	41 (16·6)	112 (19·0)	52 (14·6)

All <1750 g *v* siblings: *p<0·001, **p<0·0001

children from social classes III manual, IV, and V or with an unclassifiable social class, had higher conduct disorder scores than those from more advantaged homes.

In the 357 families where a questionnaire was available for a sibling, the study children had significantly worse scores than their siblings (p=0·001); this difference was confined to the conduct part of the score (p=0·0001). In families where the study children had high scores, those of their siblings were also high.

The examiners recorded their perception of the child's response to the test situation using the 'faults of coping style' component of the Henderson revision of the test of motor impairment.[19] Poor attention span, defined as being unable to settle for more than a short time to carry out the test items, was reported in 47% of the children. These items were grouped to reflect the same behaviours outlined in the conduct and neurotic parts of the Rutter questionnaire (M Rutter, personal communication). There was a high level of agreement between parents and examiners both on the factors reflecting the conduct score (p<0·0001) and those which corresponded to the neurotic component of the Rutter score (p<0·005).

Discussion

The normal development of language in children is an interactive process requiring in the first place intact hearing, and secondly, exposure to speech. The ability to name objects is an early stage in this development but the ability to describe situations and give clear explanations using grammatical sentences requires contact with more sophisticated speech. Where a child is perceived by the parents to be younger than he or she is, by reason of size or disability, the speech to which he or she is exposed may be tailored by adults to conform to this perception. In this study when children with a known hearing deficit affecting both ears were excluded, a relationship was found between the parents' positive response to a question asking 'do you still regard your child as premature?', and the child's performance on the language tests involving scoring of grammar. There was, however, no relationship between the child's height centile and measures of sentence length, although the other measure of grammar competence was significantly related to height.

Delays in verbal comprehension are described in otherwise normal preterm survivors and problems in phonology are reported in motor impaired children.[20] Problems of phonological awareness[21] and a poor standard of oral lanuage[22] have been identified as predictive of poor reading skills.

We found a good correlation (p=0·0001) between the verbal comprehension test in the BAS and the Renfrew information scores. Poor performance in these latter scores has been shown to be predictive of continuing speech and language deficits that are not amenable to maturational influences, suggesting that quite a high proportion of the cohort will continue to have such problems.

Low birthweight children are known to

underachieve at school, not necessarily because of lower intellectual ability.[5 10 23] Their academic failure can be secondary to specific learning difficulties which may have their origin in lesions in the developing brain.[24] Our finding that the distribution of IQ scores in this population was not directly related to birth weights is not new. Francis-Williams and Davies in 1974 reported similar data from a cohort of very low birthweight children born between 1961 and 1968 who were followed up for 4 to 12 years.[1] Using multivariate analysis the full IQ was, however, independently associated with father's social class, single parenthood, non-cephalic presentation, intraventicular haemorrhage, maternal smoking in pregnancy and, in this population, spontaneous onset of labour (table 6). The adjusted parameter estimates suggest, for example, that for children in social class I and II at birth the mean IQ is 105·6 (99·17+6·438) in the absence of other factors in the table. After standardising the scores for father's social class there was an independent effect of maternal educational qualifications on the psychometric scores.

Only 5% of the study population scored below 70 on the psychometric test; a further 3% could not be tested because of disability; the majority will be attending normal schools. Composite measures of intellectual performance, however, mask important problems associated with specific areas of intellectual ability which may affect later school competence. The visual recognition subscale, which assesses short term visual memory and visual organisational skills, was most affected, with 30% of the cohort performing below the 10th centile for the test. Together with oral language competence, these skills are among those required for learning to read, so it is likely that a proportion of the cohort will require learning support in school.

It should be noted, however, that the patterns of performance for individual subscales described in the low birthweight children were mirrored in a random sample of 100 children seen in local nurseries, except that these children had a mean intelligence quotient approximating the test mean. These different patterns of performance in the subscales and their relationship to motor performance are explored further in a following paper.

Although, like many others,[7–10] we found that a high proportion of the low birthweight children exhibited features of attention deficit, many of the other behavioural problems usually reported in such populations were not identified. The test used to identify problems was, however, originally designed for use with children of school age.[18] If the consequences of the impaired cognitive performance reported for these children means they experience later failure in school, then it may be that the behaviour problems reported in similar populations[7] will become manifest at some later stage.

Table 6 The association between maternal pregnancy and perinatal factors and overall IQ using multivariate analysis. In the absence of the factors below mean IQ is 99·17 (1 265)

	Adjusted parameter estimates (SE)
SC I+II at birth	+6 438 (1 729)
SC IV at birth	−5 156 (1 587)
SC not known/missing at birth	−7 910 (1·741)
>10 cigarettes/day	−2 786 (1 311)
Single mother at birth	−6 978 (1 656)
Non-cephalic presentation	3·686 (1 271)
Spontaneous onset of labour	−2·814 (1 205)
Intraventricular haemorrhage	−14 21 (6 779)

SC=social class

This study highlights important deficits in the performance of low birthweight children, even among those whose overall psychometric scores fall within the normal range. These specific problems are likely to have implications for their success in learning to read and in acquiring numeracy. Further assessment of the cohort is planned at 8 years of age.

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Archives of Disease in Childhood 1992; 67: 687–690

Impaired motor function (clumsiness) in 5 year old children: correlation with neonatal ultrasound scans

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Abstract

All 155 surviving children from a cohort of 200 very low birthweight infants originally studied in 1984–5 were traced. These infants had careful sequential ultrasound examinations in the neonatal period. The children were examined again at entry into school at 5 years of age. The test of motor impairment (TOMI) and the vocabulary subscale of the Wechsler preschool and primary scale of intelligence (WPPSI) were administered to 152 of the index cohort and 144 control children of the same age in the same class at school. Twelve of the cohort had cerebral palsy, but eight of these were in mainstream schools. The index group scored significantly higher on both the TOMI and the WPPSI subscale compared with the controls. The index cases were subdivided on the basis of their neonatal ultrasound scans into four groups: group 1, consistently normal; group 2, 'prolonged flare'; group 3, germinal matrix haemorrhage–intraventricular haemorrhage (GMH–IVH), without parenchymal haemorrhage, but no evidence of prolonged flare; and group 4, both GMH–IVH and prolonged flare. The group of index children with consistently normal ultrasound scans had a higher TOMI and lower WPPSI compared with their controls. There was a statistically significant increase in the TOMI subscore 1 (manual dexterity) in group 4 infants compared with group 1, but not differences between the other groups. Regression analysis suggests that neither prolonged flare nor GMH–IVH has an important individual contribution to the variation, but the low birth weight does have a significant relationship with motor impairment. It appears that relatively minor ultrasound appearances such as prolonged flare and GMH–IVH are associated with motor impairment (clumsiness) at 5 years, but this has a small effect compared with low birth weight.

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Accepted 29 January 1992

Cerebral palsy is the commonest serious neurological deficit occurring in babies who have been born very prematurely. A number of groups have reported an association between ultrasound abnormalities detected in the newborn period and subsequent cerebral palsy,[1–3] particularly cystic periventricular leucomalacia (PVL)[1] and porencephaly.[3] There is some suggestion that the ultrasound appearance we have previously defined as 'prolonged flare',[4] but also referred to as 'small intraparenchymal echodensity',[5] 'peritrigonal echogenic blush',[6] and 'echogenic periventricular halo',[7] may represent a less severe form of PVL.

We hypothesise that repeated assessment by real time ultrasound imaging detects a range of PVL injuries from severe (represented by multiple echofree cystic lesions) to moderate (prolonged flare or non-cavitating echodensity). It is probable that mild PVL will not be reliably detected on currently available imaging techniques. In 1984 and 1985 we prospectively collected a cohort of very low birthweight (VLBW) infants who had very careful and regular ultrasound scans performed throughout the neonatal period by a single ultrasonographer.[4] Definitions of ultrasound abnormalities were agreed before the study and did not change through the 16 months of patient collection. We showed that cavitating PVL correlated well with the subsequent diagnosis of cerebral palsy ascertained at 18 months corrected for prematurity.[1] In order to test our hypothesis that less severe ultrasound abnormalities may correlate with less severe degrees of motor impairment, we have examined the children from our 1984 cohort again at 5 years of age. We report here our findings relating to motor impairment at the age of 5 years. Reports of findings for other outcome variables are in preparation.

Patients and methods

Over a 16 month period from 1 January 1984, all VLBW infants (<1501 g) admitted to either the Leicester Royal Infirmary or the Nottingham City Hospital were regularly studied with real time ultrasound as previously described.[4] Before undertaking the study, definitions of ultrasound abnormalities had been agreed and all the ultrasound scans were done at both hospitals by a single operator using an ATL ultrasound machine with a 7·5 MHz transducer at least twice weekly for the first month and then every week until discharge. All babies with ultrasound abnormalities on the scan before discharge were recalled for at least one further scan.

Early ultrasound abnormalities included germinal matrix haemorrhage–intraventricular haemorrhage (GMH-IVH), and parenchymal haemorrhage (an echodense area involving the ventricle and the parenchyma). Later changes (after two weeks from birth) were described as 'cystic periventricular leucomalacia' and prolonged flare (an appearance of relative increased echodensity in the periventricular region seen in both coronal and parasagittal views, and persisting for at least two weeks and not undergoing cystic degeneration). A porencephalic cavity was diagnosed if a large echofree area involving the parenchyma and in wide communication with the ipsilateral lateral ventricle was seen. This was always unilateral.

Surviving children were examined by one neurodevelopmental paediatrician at 18 months (M Graham).[1] The present study attempted to examine all these children again at 5 years of age in their first term in full time school. The head teacher of the school was contacted and asked for permission to assess the child in school. He or she was also asked to identify from the same class a control child of the same sex and ethnic background nearest in birth date to the index child. Written permission to assess the child was obtained from the parent(s). The head teacher was asked to tell the class teacher that these two children were to be assessed, but not the reason for the assessment, nor which child was the index case.

The two children were assessed separately but in the same session by one researcher (SD). The examination comprised: the test of motor impairment (TOMI), the vocabulary scale of the Wechsler preschool and primary scale of intelligence (WPPSI) and a number of measures of basic literacy, language, representational and mathematical concepts and skills most of which were used and reported by Tizard *et al.*[8] Teachers were also asked to complete a checklist of behavioural statements.[9]

It was not possible to undertake complete neurological examinations on all the index and control children. The following children were examined by the same neurodevelopmental paediatrician who saw them at 18 months (M Graham): all children thought to be neurologically abnormal when seen at 18 months, including those who showed dystonia; all children with the ultrasound appearances of cystic PVL or prolonged flare in the neonatal period; and all children who had a high TOMI score above 10, suggesting the possibility of definite neurological abnormality.

The TOMI originally described by Stott *et al* and revised by Henderson[10] tests the child's level of skill in various motor functions. The test is arranged in four age bands, and the 5–6 year band was used in this study. The test has been recently standardised on a large number of British and North American children. The test involves eight items and for each item the child receives a score between 0 and 2: 0 denotes acceptable performance, 1 indicates borderline pass, and 2 indicates fail of that item. Thus the higher the score the less competent the child. The test includes three groups of items: manual dexterity, ball skills, and both static and dynamic balance. The maximum score for these three subscales were 6, 4, and 6 respectively. The TOMI normally took 20 minutes to administer, but could take up to 75 minutes if the child had particular difficulties. All but one of the TOMI assessments were done by the same observer. The entire assessment took an average of 75 minutes for each child.

For the purposes of this report only the TOMI and WPPSI variables are reported. Statistical analysis was done using the Wilcoxon or Mann–Whitney test on non-parametric data and by *t* test for parametric (WPSSI) data. Regression analysis was performed using the square root of the total TOMI score in order to produce a regression equation with normal residuals.

Results

Of the original cohort of 200 infants, 157 were alive at 18 months and all but one (lost to follow up) had a complete neurodevelopmental assessment at that time. One further child died at three years (he had spastic hemiplegia) and all the 155 children alive at 5 years were traced. Three of these were not, however, fully assessed at 5 years. The parents of one refused to allow her to be seen, another lived in Cyprus and we could not organise assessment, and the third was in a vegetative state with spastic quadriplegia and profound intellectual impairment and could not be assessed with the TOMI; she was, however, examined by a developmental paediatrician (M Graham). Thus, 152 of the index children (97% of those seen at 18 months) had a full range of tests at 5 years. In some cases there were problems in identifying control children, for example they may have been absent from school when the visit was arranged, and only 144 controls were fully assessed.

Fifty of the 153 children had a neurological examination by a developmental paediatrician (M Graham). The indications for examination in this group were findings of either cerebral palsy (n=11) or dystonia (n=6) at 18 months, a neonatal ultrasound diagnosis of prolonged flare (n=20), and cystic PVL in children who showed no neurological abnormality at 18 months (n=5). In addition, eight other children were examined because they had a TOMI score over 10. In all, 12 of the index children had cerebral palsy (see table 1) and eight of these were in mainstream schools and four in special schools. Of the 12 children with cerebral palsy at 18 months, one had died, and one other no longer had signs of cerebral palsy at 5 years. The signs were largely unchanged in the other 10. Two children with cerebral palsy at 5 years (No 26 and 179) did not show signs of it at 18 months. Neither of these had ultrasound abnormalities involving the cerebral parenchyma and both were reviewed because of a TOMI score above 10.

The results of the TOMI assessments and the three subscores for all index and control children are shown in table 2. The median TOMI in the index group of VLBW infant survivors was 3·25 (range 0–16) and the median figure for the controls was 1·00 (range 0–8). The statistical comparison was made only between each index child and his/her control and 144 pairs were analysed. There was a highly statistically significant difference between the total TOMI score and each of the subscores ($p<0·001$). The mean (SD) WPPSI vocabulary scale for the index group was 19·1 (6·41) and for the controls was 21·6 (6·46). These differences were statistically significant ($p=0·0007$).

The index children were subdivided into four groups. Group 1 had consistently normal ultrasound scans (n=64), group 2 had prolonged flare as the only ultrasound abnormality (n=13), group 3 had GMH–IVH as the only ultrasound abnormality and no parenchymal involvement (n=54), and group 4 infants had both prolonged flare and GMH–IVH without parenchymal involvement (n=9). Children whose ultrasound scans had shown parenchymal haemorrhage or cystic PVL were excluded from this part of the

Table 1 Details of the children with cerebral palsy diagnosed at 5 years

Code No	*Birth weight (g)*	*Ultrasound diagnoses*	*Description of cerebral palsy*	*TOMI score*	*WPPSI (vocabulary)*
3	1300	Grade II PVH and CPVL	Spastic quadriplegia[*]	16	0
26	1400	Normal	Quadriplegia	16	0
42	860	Grade II PVH and CPVL	Left hemiplegia	9·5	13
81	1380	Grade III PVH and CPVL	Left hemiplegia	16	0
125	1190	Prolonged flare	Left hemiplegia	6·5	22
126	1180	Grade III PVH and CPVL	Quadriplegia	—	—
130	1020	Grade III PVH, prolonged flare	Right hemiplegia	10·5	19
132	1440	Grade II PVH and CPVL	Diplegia, blind in one eye	16	20
157	1450	Grade II PVH and CPVL	Left hemiplegia	9	17
168	830	Grade II PVH	Double hemiplegia	13	14
177	1500	CPVL	Diplegia	11	28
179	1250	Grade I PVH	Diplegia	10	19

[*] This child was in a vegetative state and further assessment was not possible.
PVH, periventricular haemorrhage, CPVL, cystic periventricular leucomalacia

analysis. Table 3 shows the overall TOMI and the subscores for each of these four groups. There was one child each in group 1 and 2 who had cerebral palsy. Two children in group 3 had cerebral palsy and none in group 4. When the overall TOMI results were considered in the four groups there were no significant abnormalities. The children in group 4 had significantly higher scores for manual dexterity (subscale 1) than for those in group 1 with normal scans ($p=0{\cdot}033$, see table 3). The WPPSI vocabulary scales showed no statistical diffferences when these groups were compared (group 1 *v* group 2, $p=0{\cdot}27$; group 1 *v* group 3, $p=0{\cdot}88$). When children in group 1 (consistently normal ultrasound scans) were compared with their controls and for the total TOMI score there was a estimated difference (case minus control) of 1·5 ($p<0{\cdot}001$ non-parametric Wilcoxon signed rank test); and when compared for the WPPSI (vocabulary scale) an estimated difference (case minus control) of −3·0 ($p=0{\cdot}015$).

Table 2 Median (ranges) for TOMI and TOMI subscores and mean (SD) for the vocabulary scale of the WPPSI

	TOMI				*WPPSI (vocabulary)*
	Overall	*Subscore 1*	*Subscore 2*	*Subscore 3*	
Index cases (n=152)	3·25 (0–16)	1·0 (0–6)	1·0 (0–4)	1·0 (0–6)	19·1 (SD 6·41)
Control cases (n=144)	1·0 (0–8)	0·0 (0–3·5)	0·0 (0–3)	0·0 (0–5)	21·6 (SD 6·46)
p Values for cases *v* controls	<0·001	<0·001	<0·001	<0·001	0·0007[*]

The p values refer to one sample non-parametric Wilcoxon test and [*]paired Student's *t* test Subscore 1, manual dexterity, subscore 2, ball skills, subscore 3, static and dynamic balance.

Table 3 Median (ranges) for TOMI and TOMI subscores and mean (SD) for the vocabulary scale of the WPPSI

	TOMI				*WPPSI (vocabulary)*
	Overall	*Subscore 1*	*Subscore 2*	*Subscore 3*	
Group 1 (n=64) (no ultrasound abnormality)	2·25 (0–16)	0·5 (0–6)	1 (0–4)	1 (0–6)	19·3 (5·82)
Group 2 (n=13) (prolonged flare, PF)	4·5 (0·5–9·5)	0·5 (0–5·5)	1 (0–2)	2 (0–5)	21·1 (4·91)
Group 3 (n=54) (GMH–IVH)	3 (0–13)	1 (0–5)	1 (0–3)	1 (0–6)	19·2 (6·64)
Group 4 (n=9) (PF and GMH–IVH)	5·5 (1–13)	1·5 (1–4)	1 (0–4)	2 (0–6)	18·6 (7·68)
Statistical comparisons: (p values)					
Group 1 *v* 2	0·237	0·411	0·840	0·156	0·27
Group 1 *v* 3	0·260	0·429	0·930	0·184	0·88
Group 1 *v* 4	0·061	0·033	0·110	0·460	0·78
Groups 2, 3, and 4 *v* 1	0·088	0·162	0·595	0·098	0·94

The p values refer to two sample non-parametric Mann-Whitney tests and two sample Student's *t* test for the WPPSI data.

Regression analysis was initially undertaken using GMH-IVH and prolonged flare as independent variables against the square root of total TOMI score as the dependent variable. This gave a t ratio for the coefficient of prolonged flare of 1·82 ($p=0{\cdot}07$) and for GMH-IVH of 1·14 ($p>0{\cdot}1$). When birth weight was added to the model as a third independent variable, the t ratio for prolonged flare fell to 1·68 ($p=0{\cdot}1$) and the estimate of the coefficient of birth weight was negative with a value of −1·04 (SE 0·36, t ratio −2·89, $p=0{\cdot}005$). Birth weight accounted for the greatest proportion of the variation explained by the regression equation.

Discussion

It is well known that cerebral palsy is approximately 200 times more likely to occur in children who have been born very prematurely than in a group of babies born at full term. It has also been reported that children who have been born very prematurely and who show no 'hard' neurological deficits, may perform less than optimally when they start school due to a number of factors. These include behavioural problems,[11] attention deficit disorders,[12] and a group of non-specific problems referred to as 'soft neurological signs'[13] or 'minimal brain dysfunction'.[14]

We have shown that there are important differences in both motor function and measures of verbal intelligence between children who were of very low birth weight and controls when assessed at 5 years. These findings are in keeping with those of Marlow *et al* who assessed 53 children at 6 years who weighed less than 1251 g at birth.[15] They also used the TOMI to detect significant motor difficulties. The TOMI is now a well accepted objective diagnostic test for clumsiness. We may be criticised for only using the vocabulary subscale of the WPPSI test, but we were concerned that a fuller assessment of intelligence, together with all the other components of our assessment would fatigue the children. We chose a subscale of intelligence that was not motor dependent. Astbury *et al* have shown that in a group of VLBW survivors assessed at 5 years the verbal subscore of the WPPSI correlated very well with the mean performance score and the full scale score.[12]

This study has correlated relatively subtle ultrasound abnormalities with motor impairment at 5 years. We have shown a statistically significant relationship between the scan appearances of both GMH-IVH with prolonged flare and subsequent impairment of manual dexterity. There is some correlation between the appearance of non-cavitating echodensity (defined by various authors in different ways[4–7]) and necropsy specimens, suggesting that this appearance is 70–81% accurate for PVL.[6 16] It is now well accepted that cavitating abnormalities within the cerebral parenchyma recognised with ultrasound imaging correlate with the development of cerebral palsy,[1–3] but there are no data on the more subtle ultrasound abnormalities and less severe forms of central motor impairment. We have previously shown that cystic PVL diagnosed by ultrasound strongly correlated with the subsequent development of cerebral palsy,[1] but this most recent report adds little weight to the hypothesis we had previously suggested that prolonged flare represented a less severe form of injury to the periventricular white matter. It will be necessary to follow up much larger groups of premature infants with the appearances of prolonged flare to know whether this feature is actually a marker of subsequent development of clumsiness. We only compared children with no evidence of major parenchymal abnormality to avoid the possibility that these lesions are likely to have a very large effect on the overall TOMI score, thus swamping more subtle effects of 'minor' ultrasound scan abnormalities.

It is unfortunate that not all the VLBW infants had a neurological assessment at 5 years, but this was not logistically possible given the budget of this project. In all, one third of the index children were examined. It is of interest that one child found to have cerebral palsy at 18 months neither showed abnormal neurological signs at 5 years, nor did she have a high TOMI score. Two children who were thought to be normal at 18 months were found to have cerebral palsy on neurological assessment. Both these were undiagnosed by their medical attendants and were picked up by a very high TOMI score.

One of the most interesting findings in this study, and one that has not been reported before, is that those children who had been born of VLBW and who had consistently normal ultrasound scans had significantly higher TOMI and lower WPPSI (vocabulary) scores compared with controls. It is possible that ultrasound invisible haemorrhagic or ischaemic lesions were present but were not severe enough to account for these deficits. We believe that this is somewhat less likely than an alternative hypothesis that there was neuronal loss as the result of other factors such as undernutrition,[17] subclinical hypoglycaemia,[18] or lack of early learning opportunities. These variables deserve further investigation.

Wariyar *et al* have criticised follow up studies that have failed to study all children in a cohort and they showed that those children who were most difficult to find were the ones who were most likely to have significant disability.[19] We identified 99·5% of all the children known to be alive at 18 months of age and examined all but two of these. It is unlikely that results from the two missing children would significantly alter our conclusions.

In summary, we report the association between the ultrasound appearance of GMH–IVH and prolonged flare on the one hand and motor impairment or clumsiness on the other. This association is very dependent on low birth weight; it appears that the risk of motor impairment is most closely related to increasingly low birth weight. The motor impairment may cause significant difficulties at school and may be a feature of later learning problems.[20]

We are very grateful to Action Research for the Crippled Child for financial support of this project and to all the schools and parents who cooperated with us. The high response rate owes much to the organisational skills and tactful perseverance of Julia Thomson.

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Archives of Disease in Childhood 1992; 67: 691–692

Postdischarge formula consumption in infants born preterm

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Abstract

In 31 infants born preterm and formula fed ad libitum, all milk intake was weighed from hospital discharge to nine months post-term. Mean daily milk intake was high, reaching 230 g/kg before four weeks post-term and was still over 150 g/kg beyond six months. Five of the 31 infants (16%) consumed 300–350 g/kg; 50% 'voluntarily' consumed more than upper recommended limits for energy intake and 35% did so for protein intake.

Despite considerable research on nutrition of preterm infants, there is little scientific information on their nutritional management after discharge from hospital. One practical question is how much milk should formula fed preterm babies consume during infancy? Their ad libitum milk intake might not be the same as in a full term baby. Preterm infants frequently show appreciable postnatal growth deceleration and often leave hospital with considerable catch up growth to achieve. Furthermore, enteral feeding is often given many weeks too soon in biological terms by an unphysiological route and in larger volumes (per kg) than those usually received by full term babies. We speculate these factors could influence the normal development of feeding behaviour. In 31 infants born preterm we weighed entire milk intake from hospital to nine months post-term and related milk intake to demographic factors.

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Accepted 20 January 1992

Subjects and methods

Preterm infants, whose mothers had chosen not to breast feed, were randomly assigned a standard adapted formula (Ostermilk, Farley Health Products Ltd) and a new, nutrient enriched 'postdischarge' formula (Premcare, Farley Health Products Ltd). The trial results will be published elsewhere; this paper concerns only weighed milk intake data. Milk intake on the two formulas was very similar and both formulas had a composition (energy 68 or 72 kcal/100 ml (285 or 301 kJ/100 ml); protein 1·5 or 1·8 g/100 ml) within the range recommended in Britain.[1] These formulas reflect the range of nutrient contents likely to be used in this population. Therefore we combined data from the two feed groups.

Mean (SE) birth weight was 1480 (200) g and gestation 31 (2) weeks (maxima: 1850 g and 35 weeks). Patients were recruited while in hospital (with informed consent and approval of the Cambridge Health Authority and Medical Research Council's local ethical committees) and studied after discharge home. At study entry mean (SE) postmenstrual age was 38 (3) weeks and mean (SE) body weight 2000 (190) g. Extensive clinical and demographic data had been collected during hospital stay.

In the home preweighed bottles of 'ready-to-feed' formula were supplied to the mother. Teats were attached to the bottles for feeding and at the end of the feed the teat was removed, the cap tightly replaced, and FK reweighed all bottles after each two week period up to nine months post-term. Regurgitations were not recorded as our objective was to measure intake rather than retention. Formula was consumed exclusively for a median of 11 weeks and then with weaning foods.

Results

Table 1 shows centile data for formula intake from discharge to term and for each four week period up to 40 weeks post-term.

To explore whether the babies who consumed the greatest milk volumes were the most immature or growth retarded, gestation and body weight SD score at discharge from hospital was correlated with milk intake/kg body weight for the first five postdischarge age periods studied (table 2).

Table 1 Weighed milk intake (g/kg/day): median and interquartile range (raw data), smoothed 97th centile (estimated from SD) and, for comparison, 97th centile for full term infants estimated from reference data (Fomon et al[5])

Weeks post-term	*Median*	*Interquartile range*	*Smoothed 97th centile*	*(97th centile for term infants)*
Discharge to term	212	189, 227	272	
1–4	230	195, 254	322[*]	(220)
5–8	206	170, 234	303	(204)
9–12	175	157, 203	286	(177)
13–16	177	143, 216	270	(166)
17–20	156	134, 187	255	
21–24	152	123, 183	240	
25–28	142	123, 182	227	
29–32	120	105, 145	215	
33–36	104	89, 138	203	
37–40	102	82, 129	191	

[*] Highest individual value 353 ml/kg/day.

Table 2 Correlations of gestation and body weight SD score at discharge with postdischarge formula volume intakes

Age post-term	*Correlation coefficient (r) for relation between milk intake and*			
	Gestation		*Discharge weight SD score*	
	r	*p Value*	*r*	*p Value*
Discharge to term	0·24	0·23	−0·30	0·13
1–4	0·31	0·09	−0·23	0·22
5–8	0·10	0·60	−0·19	0·33
9–12	0·02	0·92	−0·09	0·64
13–16	−0·07	0·69	−0·00	1·00

Discussion

We have not identified other studies in which all formula consumed was measured over such a prolonged period in preterm infants after discharge from hospital. We observed surprisingly high volume intakes on a body weight basis. In our previous studies on exclusively formula fed full term infants from the same catchment area, milk intakes at 4–6 weeks and 10–12 weeks were 170 and 155 g/kg/day.[2] Preterm infants maintained an average intake well above this, reaching 230 g/kg in the first month post-term. Butte et *al* found that by four months milk intake in predominantly formula fed term infants had fallen to 118 g/kg/day compared with 184 g/kg in our preterm infants.[3] Intakes remained above 150 g/kg beyond six months when our (unpublished) observations show babies born at term consume under 60 g/kg/day.

Our previous work on full term infants showed mean values for weighed formula intake minus weighed regurgitations and spills were within 98–99% of the values not accounting for regurgitation.[4] We accept that preterm infants might have regurgitated more than term infants in the very early weeks, though this would be less likely to explain persistently high intakes after a few months. Carelessness was an unlikely source of significant error as our previous studies on similarly well motivated and supervised mothers showed mean weighed milk intake matched closely with intake derived by deuterium kinetic studies in the infant.[4]

Some preterm infants had particularly high intakes: 5/31 had at some time an intake over 300 g/kg. Formula intakes in full term infants have also been reported to be highly variable,[5] though the 97th centiles for intake/kg (estimated from published reference data[5]) are still substantially below those for preterm infants in the first four months (table 1). Table 2 does show some evidence for a trend (not significant) towards more immature babies and those more growth retarded at discharge having the highest intakes, but only in the early weeks. A larger sample would be needed to investigate reasons for the high intakes observed.

Regardless of mechanism, our findings have important implications for the nutrition of infants born preterm. About 50% of infants studied 'voluntarily' consumed more than the generous upper limit for energy intake for premature infants set down by the European Society for Paediatric Gastroenterology and Nutrition (ESPGAN)[6] in 1983 of 165 kcal (690 kJ)/kg (most authorities recommend 120–130 kcal (502–544 kJ)/kg/day[7]). Perhaps more important, 35% of these preterm infants consumed more than the upper limit (ESPGAN) for protein intake of 4 g/kg/day.[6] Are these babies trying to tell us something about their dietary needs?

We thank Farley Health Products Ltd for financial support and supply of diets and Evelyn Smith for preparation of the manuscript.

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Archives of Disease in Childhood 1992; 67: 693–696

Computed tomography findings in partial seizures

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Abstract

The computed tomography findings in 82 children with partial seizures of unknown aetiology were reviewed. All had seizures with predominantly focal motor phenomena and none had abnormality on neurological examination. Findings on computed tomography were normal in 64 children (78%) and abnormal in 18 children (22%). Fourteen children had changes representing static pathology (mainly cerebral atrophy) which did not influence patient management but four had potentially correctable lesions (two tumours and two arteriovenous malformations). There were no correlations between seizure control, seizure duration, intellectual handicap, postictal weakness, electroencephalographic findings, and abnormality on the computed tomogram. In particular, none of these features were useful in predicting the presence of a tumour or arteriovenous malformation. It is concluded that a computed tomogram is indicated in every child wtih partial seizures.

The value of computed tomography in the investigation of epilepsy depends to a large extent on seizure type. For example, a low incidence of abnormality is found in primary generalised epilepsy[1–3] and benign rolandic epilepsy[4] but an abnormal computed tomogram is common in children with infantile spasms.[5 6] In the investigation of partial seizures, few paediatricians would hesitate to ask for a computed tomogram if other neurological symptoms or signs were present. In their absence, the indication for computed tomography has been less certain. A recent onset of partial seizures in an adult without other clinical features raises concern about a possible space occupying lesion. Although it is acknowledged that the same event in a child is less likely to be due to sinister intracranial pathology,[2] there are few data on the incidence of abnormal scans in children who present with partial seizures alone. Previous studies have tended to group together children with neurological signs, children without neurological signs, and children with known seizure aetiologies.[7–11]

In order to investigate the incidence of abnormal computed tomograms we have reviewed 82 children seen at Leeds or Bradford who had neither neurological signs or symptoms nor known aetiology for their partial seizures. Possible indicators of abnormality were sought by examining correlations between seizure duration, seizure control, findings on an electroencephalogram (EEG), postictal weakness, intellectual handicap, and findings on computed tomography.

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Accepted 15 January 1992

Patients and methods

Although partial epilepsy can produce a variety of symptoms, we chose to review only those children whose seizures had predominantly focal motor phenomena rather than select patients on the basis of focal EEG abnormalities. This decision was based on the assumption that focal motor symptoms cause more concern about a possible structural lesion than other epileptic symptoms. For the purpose of this review, we did not differentiate between partial seizures of elementary symptomatology and partial seizures of complex symptomatology.

The 82 children presented between June 1978 and November 1988. Their age at onset of seizures ranged from 5 months to 14 years (mean age 5 years). All the children had partial seizures with well documented focal motor phenomena. Fifty one children had partial seizures only; 21 presented with partial seizures but later had generalised seizures; and 10 children presented with a generalised seizure but later had predominantly partial seizures. Six children had a history of febrile seizures which were prolonged in two cases.

Children with a known or suspected aetiology were excluded from the study. Children with severe mental retardation were excluded but not children with specific learning difficulties, mild or moderate mental retardation, or behaviour problems. Although none of the children had neurological abnormalities on examination, 18 children had brief transient focal weakness in the immediate postictal period. Children with benign rolandic epilepsy were not included because the absence of an underlying structural lesion is well recognised.[4]

In Leeds General Infirmary, computed tomograms were initially performed on the EMI 1010 scanner and later on an IGE 9800 scanner. In Bradford Royal Infirmary, a Siemens Sonaton DR third generation scanner was used. Six children had repeat tomograms and four children had angiography. All children had at least one EEG. Thirty five children, at the time of writing, have had one or more repeat EEG. In examining possible correlations between seizure duration, seizure control, intellectual handicap, EEG findings, and an abnormal computed tomogram, the χ^2 test was used.

Results

The findings on computed tomography, which

Table 1 Findings on computed tomography in 82 children with partial seizures

	No of children
Normal	64
Focal atrophy	5
Bilateral atrophy	4
Bilateral atrophy with calcification	1
Bilateral calcification	1
Focal calcification	1
Focal cortical enhancement	1
Infarction	1
Tumour	2
Arteriovenous malformation	2
Total	82

are shown in table 1, were normal in 64 children (78%) and abnormal in 18 children (22%). Three of the latter group, one of whom showed bilateral atrophy, one bilateral atrophy with calcification, and one an old infarct, had normal tomograms initially. There was no significant difference in mean age for those with normal and those with abnormal scans (5·2 years and 4·8 years respectively). Ten of the abnormal tomograms showed atrophic changes, the commonest abnormality being focal atrophy. Four children had varying degrees of bilateral atrophy ranging from slight ventricular enlargement suggesting central atrophy to generalised cerebral atrophy. The child with bilateral atrophy and calcification was neurologically normal when he presented with partial seizures at 1 year but three months later developed rapidly progressive developmental regression and intractable seizures, suggesting a neurodegenerative disorder. Extensive investigation did not produce a specific diagnosis, and when he died two years later permission for necropsy was refused. The computed tomograms of two children showed calcification of the type found in the incomplete Sturge–Weber syndrome.

Table 2 Number of children with prolonged seizures, difficult to control seizures, intellectual handicap, and postictal weakness

	Normal tomogram	*Abnormal tomogram*	*p Value*
Prolonged seizure	21	7	>0·5
Difficult to control seizures	20	3	>0·1
Intellectual handicap	13	6	>0·5
Postictal weakness	14	4	>0·5

Table 3 EEG findings in children with normal and abnormal computed tomograms (figures in brackets are findings when all EEG findings are taken into account)

Initial EEG finding	*Normal tomogram*	*Abnormal tomogram*	*p Value*
Normal	32 (26)	8 (6)	>0·5
Focal spike and wave	19 (23)	8 (8)	>0·1
Focal slow waves	1 (1)	1 (2)	>0·5
Generalised spike and wave	7 (8)	1 (2)	>0·5
Bilateral slowing	5 (6)	0	>0·5
Total	64 (64)	18 (18)	

Table 4 Features of the four children with structural abnormalities on computed tomography

	Age at presentation (years)	*Prolonged seizure*	*Difficult to control seizures*	*Intellectual handicap*	*Initial EEG*
Meningeal fibrosarcoma	13 5	No	No	No	Normal
Astrocytoma	1	Yes	No	Yes	Normal
Arteriovenous malformation	6 8	No	No	No	Slow waves
Arteriovenous malformation	9	No	No	No	Normal

Although most of the abnormalities on computed tomography suggested static pathology, four children had structural lesions which were of therapeutic significance. Two children had tumours which were managed surgically: one tumour was found to be an astrocytoma of the right parietal lobe and the other a meningeal fibrosarcoma of the right parietal lobe. One child had an arteriovenous malformation of the left parietal region which was treated surgically. The other child with an arteriovenous malformation which involved the right presylvian fissure has been managed conservatively, although it is planned to treat this lesion by means of stereotactic radiotherapy. In both cases, the arteriovenous malformation was confirmed by angiography. In neither case was an intracranial bruit present. None of the four children with structural abnormalities complained of headache.

Approximately one third of all the children had one or more prolonged seizures of more than 30 minutes' duration, and approximately a quarter had seizures which were difficult to control. There were no statistically significant differences in the occurrence of prolonged seizures, difficult to control seizures, intellectual handicap, and transient postictal weakness between children with normal and abnormal tomograms (table 2).

Initial EEG findings are shown in table 3. Forty of the children (49%) had normal initial EEG recordings. Almost the same incidence of abnormality on computed tomography (20%) was found for children with normal initial EEG recordings as for all children in the series. Focal spike and wave was the commonest single abnormal finding. Focal slow waves, often taken as suggesting an anatomical abnormality, were present initially in one child with an abnormal computed tomogram. Of the eight children whose initial EEG recordings showed generalised spike and wave, six had partial seizures and only two had partial and generalised seizures. There were no statistically significant differences in any of the EEG findings between children with normal and abnormal computed tomograms. At the time of writing, 35 children have had one or more repeat EEG recordings. This slightly increased the number of the children with focal spike and wave but did not influence the p values.

The clinical features and EEG findings of the four children with structural abnormalities are shown in table 4. One child had a prolonged seizure, one had postictal weakness, and none had difficult seizure control. Both children with tumours and one of the children with an arteriovenous malformation had normal EEG recordings; the latter had three normal EEG recordings.

Eleven children with initially normal computed tomograms had intractable seizures. Five of them had repeat tomograms of which three were normal, one showed generalised atrophy with calcification, and one showed an old infarct. Two children, in the early years of the study, had normal angiograms. The remaining four children have not yet had repeat scans. However, their tomograms were taken relatively late—on average seven years after the onset of seizures. Another child in the series who had a normal initial computed tomogram was reinvestigated because of deteriorating performance at school. His repeat tomogram showed bilateral atrophic changes.

Discussion

This present study was confined to a review of children with partial epilepsy whose predominant seizure type was focal motor in nature. Children with abnormalities of the central nervous system and children with known or suspected aetiologies for their seizures were excluded. Not unexpectedly, we found that the majority of the children in our study had normal computed tomograms. Most of the children with abnormal tomograms had changes representing static pathology but four children had lesions of therapeutic significance. In drawing comparisons with previous studies, it is important to be aware that many of these studies included children with seizure types other than partial, children with abnormalities on neurological examination, and children with known or suspected aetiologies for their seizures.[7–11]

In partial epilepsy, the frequency of abnormal findings on computed tomography is age dependent. Angeleri *et al* found abnormalities on computed tomography in 10% of childhood cases compared with 29% for patients between 19 and 50 years and 59% for patients over 51 years.[12] The incidence of brain tumour is increased when partial epilepsy has its onset in adulthood.[2]

Lagenstein *et al* in a study of tomography findings in 309 children with different types of epilepsy, found that 64 (39%) of 165 children with partial epilepsy had abnormal tomograms.[10] Most of these changes were atrophic and only one child had a tumour. Yang *et al* found that 50% of 34 children with partial seizures of elementary symptomatology and 30% of 46 children with partial seizures of complex symptomatology had abnormal tomograms.[9] Although focal atrophy was the commonest finding, four children had tumours. Both the series of Lagenstein and of Yang included children with abnormal neurological findings which may explain the higher incidence of abnormality than found in our study. Yang *et al* found that children with partial seizures and abnormal neurological findings were a high yield group, 65% having abnormal findings.[9]

In a review of the findings of 115 epileptic children without neurological signs or symptoms, Patel *et al* found that nine out of 37 children (24%) with partial epilepsy had abnormal tomograms.[13] Of these nine cases, two had atrophy, four had infarction, two had porencephalic cysts, and one had an arachnoid cyst. None of these cases required surgical intervention and, although the number of children with partial seizures was relatively small, Patel concluded that computed tomography could be excluded from the investigation of children with seizures alone. A similar view was expressed by Harwood-Nash who reviewed the tomographic findings of 695 epileptic children.[14] However, he did not divided the children into seizure types.

In common with other authors,[9 10] we found that atrophy was the commonest abnormality. It is interesting that six of the 18 children with abnormal tomograms had bilateral changes. Gastaut comments that this is not a rare finding in partial epilepsy because certain diffuse brain lesions can induce partial seizures due to the predominance of histological abnormalities in regions with a low seizure threshold.[2] Although the finding of atrophy may suggest an earlier insult such as perinatal hypoxia and might possibly have prognostic value, it does not usually influence patient management. Although we did not find any cases of tuberose sclerosis, this condition was found in three children in the series of Yang *et al*[9] and one child in that of Lagenstein *et al.*[10] This finding has important prognostic and genetic implications.

One of the main reasons for carrying out computed tomography is to exclude a neoplasm or other treatable lesion such as an arteriovenous malformation. Although these lesions are likely to present in a small minority of otherwise neurologically normal children, we had four children (5%) with potentially correctable lesions. With the possible exception of focal slow waves in one case, there were no reliable pointers to the presence of these lesions.

Prolonged seizures, difficulty with seizure control, intellectual handicap, and postictal weakness were as common in children with normal tomograms. It is noteworthy that three of the children with structural lesions had normal EEG recordings. Surprisingly few of the 18 children with abnormal tomograms had slow waves. Yang found that patients with focal slowing showed a significant increase in abnormality.[9] Sixty three per cent of his cases with focal slowing had abnormal tomograms.

We would disagree with the conclusions of Patel *et al*[13] and Harwood-Nash[14] that computed tomography should be reserved for children with seizures plus abnormality on neurological examination. We would agree with the view expressed by Wylie *et al* in their recent review of partial seizures that computed tomography is indicated in essentially all children with partial seizures.[15] There have been several reports of unsuspected tumours or other structural lesions in children diagnosed by tomography.[7 16–18] For example, Holmes described two children, one with a glioma and the other with an arteriovenous malformation, both of whom had normal neurological examinations and EEG recordings.[17] Most of the tumours described in such cases have been slow growing gliomas so that the presence of seizures for several years does not preclude the need for neuroradiological investigation.[19] As tumours have also been found in some patients after an initially normal computed tomogram,[19 20] further investigation either by repeat computed tomogram or by magnetic resonance imaging should be considered if seizures prove to be intractable.

As a means of neuroradiological imaging, magnetic resonance imaging (MRI) is technically superior to computed tomography and has the added advantage that ionising radiation is avoided. Tumours, especially low grade astrocytomas, have been demonstrated on MRI when tomograms have been normal.[21] However, MRI is often less readily available than computed tomography and is more expensive.[22] It is unlikely to supersede computed tomography for some time as the initial standard neuroradiological investigation. We would advocate that all children with partial seizures should have a computed tomogram; but if seizures prove to be intractable in children with a normal tomogram, MRI should be considered as an alternative to repeated tomography.

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Difficult and unlikeable parents

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Accepted 15 February 1992

Abstract

Children of parents who are perceived as difficult or unlikeable are at risk of receiving less good medical care. Therefore a postal questionnaire was sent to 100 hospital doctors dealing with children asking which features made them consider a parent to be difficult or unlikeable. Seventy eight responded.

Most problems arose from parents who displayed aggression, disparagement of their child, unacknowledged anxiety, or fixed ideas about the medical condition and its management. Other unpopular parental features were poor compliance, failure to listen, and the attendance of more than one accompanying adult.

Respondents graded 16 features in order of their detrimental effect on the child's care. A major factor was if the child had a condition for which the doctor could offer no treatment; less important was the fact that the child might have a condition not understood by the doctor. Parents originating from the Indian subcontinent posed additional problems, in particular the common unavailability of interpreters.

Doctors of all grades understood why parents behaved in awkward ways, but lacked strategies for dealing with them. A similar survey of nurses and therapists produced a poor response (51% returns). Only the most senior acknowledged that some parents were difficult or unlikeable and that, as a consequence, the child's care might be affected. Nurses acknowledged difficulty with parents who were violent or who abused their children physically.

A pilot survey of 25 doctors who worked in a hospital to which children were admitted showed that all the doctors considered that a child's health care was likely to be worse if the parents were perceived as 'difficult' or 'unlikeable'. House officers were likely to spend less time with the parents and to see less of the child when such parents were present. Registrars and consultants were likely to spend less time with the family at outpatient clinics and were less likely to make follow up appointments for the child. Most doctors believed that the health service for children, and the help for the individual child, would be less effective and that compliance would be poorer (in the same way that studies have shown that compliance is poorer when the patient perceives the doctor as difficult or unlikeable).

Therefore a survey was undertaken of 200 medical and nursing staff to identify the factors which caused them to regard the parents of a child patient as difficult or unlikeable.

Table 1 Sociodemographic features

Female
Male
Much older than myself
Much younger than myself
Much wealthier than myself
Much poorer than myself
Much cleverer than myself
Much less clever
Of white English origin
A northerner
A southerner
Of West Indian origin
Of Indian subcontinent origin

Method

A questionnaire was sent, together with an explanatory letter, to 100 doctors working in the four different hospitals in Leeds to which children were referred as both outpatients and inpatients. The questionnaire sought initial details of the grade of the doctor, sex, length of experience after qualification, and the proportion of the doctor's patients who were aged under 16 years of age. The doctors were allowed to remain anonymous if they wished (which few did). In addition the doctor was asked to specify if he or she had specific paediatric qualifications such as the Diploma in Child Health or the MRCP (Paediatrics).

The key question on the form was: 'Which features cause you to feel that a parent, of a child, is difficult or unlikeable (in the context of your consultation or work)'? The second section of the questionnaire asked the respondent to signify whether certain 'general features' of a parent tended to make him/her regard that parent as difficult or unlikeable. The respondent could choose between 'No effect', 'Slightly', or 'Definitely'; 13 sociodemographic features were listed (see table 1).

Two additional questions related to the child's illness: the respondent being asked if the parent seemed more difficult or unlikeable firstly 'If the child has a condition I do not understand' and secondly 'If the child has a condition for which I can offer no definite treatment'.

A similar questionnaire was sent to 100 nurses and therapists in the same hospitals as the doctors.

Results

Forms that were fully completed and returned came from 78 doctors, of whom 32 were consultants. Table 2 shows that over half of the

Table 2 The medical grade of the 78 responding doctors and the proportion of their patients who were children

Proportion of patients <16 years of age (%)	*Doctor's grade*		
	Consultant	*Registrar*	*Senior house officer*
>90	17	15	12
40–90	0	0	0
<40	15	10	9
Total	32	25	21

respondents worked all, or nearly all, of their time with children—they were mainly paediatricians but included a small number of child psychiatrists and paediatric surgeons. Those for whom children comprised a minority of their patients included dermatologists, ear, nose, and throat and orthopaedic surgeons, and accident and emergency doctors.

WHICH FEATURES CAUSE YOU TO FEEL THAT A PARENT, OF A CHILD, IS DIFFICULT OR UNLIKEABLE (IN THE CONTEXT OF YOUR CONSULTATION OR WORK)?

Most respondents mentioned at least three or four features, often giving specific examples. Nearly all of the features mentioned can be fitted into one of the nine headings listed below. Explanation of these headings, together with examples, are given.

(1) Aggression

It was rare for doctors to feel threatened physically by parents, but the majority resented parents who were combative or blaming in their approach to the doctor. An example given was when the doctor welcomes the patient saying 'Hello, what's the matter, how can I help you?' and the parent responds 'You're the doctor—you tell us'. Doctors complained about 'Parents who make it clear that they regard doctors as people who are more likely to do harm than good' and about 'Parents who give you the impression that it is your fault that the child is unwell' and keep stating 'Something must be done'.

(2) Disparagement of the child

Many doctors were influenced adversely by parents who spoke disparagingly of the child in the child's presence. This ranged from parents, of children who wet their beds, who referred to their children as being 'lazy and smelly', to those who spoke of their child as being 'evil and just like his father'

(3) Pressure for priority

Examples of this unwelcome behaviour by parents came mainly from surgeons. Typical is the comment of one, 'One of our major problems is the parent who wishes the child to have the operation in such a way that no time is lost from school, and that plans for holidays, birthday parties, school trips or the Tuesday evening Brownie meeting should not be upset. This type of parent is never off the phone, changes appointments at very short notice, cancels admission dates and yet still expects priority treatment; an impossible situation of impasse arises resulting in deferment of treatment to the child's detriment'. Respondents were sympathetic to parents who had a child with a serious condition who pleaded for priority treatment, but were adversely affected by parents who pleaded for priority when, from the doctor's viewpoint, no case for priority existed.

(4) Non-listening/poor compliance

Most doctors seemed to feel that, when they had spent time listening carefully to the parent's story of the child's problems and had been asked a lot of questions, the parent ought to be willing to listen to what the doctor had to say: 'I can't stand those mothers who continued to ask a lot of questions, one after the other, and yet never wait for a single answer'. Another doctor resented 'Parents who demand regular prolonged consultations, but persistently fail to act on the advice given'. A surgeon cited 'Parents who do not follow the advice offered at a previous consultation, and are unhappy with the results of the treatment, which was not followed'. Poor compliance with treatment was a feature that was frequently mentioned as causing a doctor to view a parent as difficult or unlikeable.

(5) Fixed ideas

'When parents' expectations are for a particular test or a particular treatment, and what I have on offer is a little better understanding and some management strategies which may or may not help'. Another paediatrician found parents difficult 'Who come to clinic certain that they know the cause of the problem, and refuse to consider other suggestions even after what seems to be a reasonable discussion and explanation'. Several doctors mentioned the scientific gulf between medical knowledge about disease and the cultural and neighbourhood beliefs for the cause of illness, leading to irrational and unproved treatments, and the inability of many parents to realise that treatments based on controlled trials or lengthy experience had increased validity.

(6) Unacknowledged anxiety

This linked with many of the other features mentioned. Doctors seemed to be more sympathetic to parents who expressed their feelings and worries than those who disguised them. One doctor recounted a consultation in which a nephrectomy was advised for a 6 year old girl. She had come to the clinic dressed in nurse's uniform, clutching a toy medical set, and was absolutely delighted by the ambience of the hospital and was hoping to have a chance to stay in the hospital. During the discussion about future surgery, the mother went into a detailed explanation about it not being possible because 'Jennifer would be so worried about being in hospital'. Doctors often had problems dealing with families where 'It is apparent that much of the problem is due to abnormal parental anxiety, but I am not able to communicate this successfully to the parents'.

(7) Accompanying friends and relatives

Doctors found it easiest to like a parent who came alone with the child, rather than one who came with a spouse, a grandmother, or a friend (termed as 'hangers on', by one paediatrician). Grandmothers were cited as being particularly irritating when they did not allow the mother to give the history or answer questions and if they were forever interrupting or trying to take possession of the child. Most of the paediatricians were more comfortable talking with one parent than trying to conduct a session with a family. It was not clear whether they felt threatened by the family or whether they were confused and unsure whom to address.

(8) Doctors' families

These were mentioned less than some might have expected. A few doctors mentioned the particular complexity of dealing with colleagues' children, but the additional difficulties of dealing with such families were balanced by the doctor feeling flattered at being selected by a colleague to help with their child.

(9) Specific terms of speech

Many doctors were irritated by specific phrases or expressions that parents used about their children. The expressions that irritated were mainly ones that involved over indulgence and a sort of 'kiddie' speak involving over use of 'tiny' and 'little' as well as pretty euphemisms for the genitalia. (I was reminded of Richard Asher quoting a mother: 'He draws up his little legs, doctor, and his little face is all screwed up when he passes his little motion'.[1])

ANALYSIS OF GENERAL FEATURES

The responses were analysed in relation to the grade, sex, experience, and qualification of the responding doctor. The numbers did not allow significant differences to emerge according to the sex or qualification of the doctor or to the proportion of the doctor's patients who were children. There were some differences according to the grade and experience of the doctor and for the purpose of presentation the senior house officers and registrars are grouped together as 'juniors' to compare their responses with those of the consultants. Less than 20% of either consultants or junior doctors were influenced significantly by the following parental features: sex, origin from the north of England (where Leeds is situated) or from the south, or whether the parent was much older or younger than the doctor. The fact that the parent was much poorer than the doctor did not make that parent more difficult or unlikeable for most doctors. Hardly any doctor admitted to any of the features making a parent 'definitely more difficult', but nearly all indicated one or more factors that made a parent seem 'slightly more difficult and unlikeable' (table 3). Indian referred to parents originating from the Indian subcontinent who, in Leeds, come mainly from Pakistan, though there are substantial numbers of Indian and Bangladeshi families also. Most doctors made clear that the reason why they found such parents difficult or unlikeable was because of communication problems primarily resulting from lack of interpreters. The different cultural beliefs and lifestyle posed lesser problems. The West Indian community, who have been living in Leeds for many years, mainly originated from St Kitts. The West Indian parents posed no problem with regards to language but several doctors indicated the difficulty they had in coping with the 'laid back attitude' of some parents and what seemed to the doctor as erratic and casual keeping of appointments. It is relevant that over 90% of the doctors were white and that none were black.

Table 3 Proportion (%) of senior doctors (consultants) and junior doctors (registrars and senior house officers) who found a particular parental characteristic difficult or unlikeable

	Consultants (n=32)	*Juniors (n=46)*
Indian	67	46
Much less clever	47	46
Much more clever	43	60
West Indian	40	28
Much wealthier	37	49
Older:younger	Less than 20	
North south		
Male female		
Poorer		

Table 4 Percentage of doctors who found a parent more difficult or unlikeable 'if the child has a condition I do not understand' and 'if the child has a condition for which I can offer no definite treatment'

Nature of child's condition	*Consultant (n=32)*	*Juniors (n=46)*
Not understood	63	83
No definite treatment	77	44

THE CHILD'S CONDITION

Doctors of all grades found the parent more difficult or unlikeable if the child had a condition which the doctor did not understand (table 4). Juniors found this significantly more upsetting than consultants ($p<0{\cdot}05$). Whereas 'If the child has a condition for which I can offer no treatment' significantly more consultants were upset than junior doctors ($p<0{\cdot}05$).

ADDITIONAL RESPONSES

Several doctors took the opportunity to write explaining their responses, and several suggested other inquiries that ought to be made in relation to the quality of doctor-family consultations. One junior doctor wrote 'It is usually the circumstances that surround a particular consultation that make it difficult for me to deal optimally with parents. Particularly [if I am] feeling ill, [with] headaches and colds, lack of sleep, or hungry'. Another paediatric registrar summed up the feeling that several expressed 'Finally I try to remember that while I am not going to like every parent that I meet, not all of them are going to like me'.

THE NURSES' AND THERAPISTS' QUESTIONNAIRE

Their questionnaire was identical to that of the doctors apart from having an additional initial question: 'If the parents are difficult or unlikeable the health care received by the child is likely to be (1) unaffected, (2) slightly less good, (3) considerably less good'.

The response rate was poor—51 completed questionnaires out of 100. It became apparent that part of this poor response was because, in some departments, the senior nurse considered the questionnaire improper and encouraged the staff to disregard it. The length and quality of the responses were also disappointing in that very few of the nurses took the opportunity to write lengthy comments in the way that had been hoped (and as the doctors had). Even though the nurses were encouraged to remain anonymous, many gave the impression that they were trying to give an acceptable answer rather than express their personal feelings. Thus, of 36 responding nurses, only six thought that the care received by the child was likely to be affected by a parent being difficult or unlikeable. That response was countered by a senior children's trained nurse with over 20 years experience who wrote 'If a parent is aggressive or over-critical, no matter what the reason, it puts the nurse on the defensive and thus reluctant to involve him/herself with the family. It is something one learns to cope with and I do not find it a big problem now, due to my lengthy experience, so I hope that it makes my care of the child only slightly less good. More junior nursing staff, however, do not cope well under that sort of pressure and avoid the child if the parents are around'. Few of the nurses indicated that any of the general features made them consider the parents difficult or unlikeable. When asked specifically what features made a parent difficult or unlikeable, several did respond mentioning the following factors:

(1) Aggressive and violent. Several nurses felt physically threatened by abusive, aggressive and, sometimes, drunk parents particularly when on duty alone at night.

(2) Child abusers.

(3) Parents who demanded preference and who were inconsiderate of other children on the ward.

Responses came from 15 therapists (dietitians, physiotherapists, occupational therapists). All except three considered that the child's care was less good if the parents seemed difficult or unlikeable. Their list of specific problems causing them to regard a parent as difficult or unlikeable was similar to that of the doctors, though they were rather more irritated by parents who failed to keep appointments or who failed to comply with treatment.

Discussion

There have been many investigations of patient satisfaction with health services and with encounters with doctors.[2–7] Several have demonstrated the need of patients for both technical excellence and doctors whose personalities are sympathetic and helpful.[5–7] In the last 20 years there has been a trend for patients to seek a sympathetic listening doctor and to be less satisfied by doctors with a more didactic approach.[8 9] The surveys are a reminder that the practice of medicine is an art as well as a technical exercise. Recent investigations confirm that the patient's satisfaction is closely related to the patient's perception of the outcome of the medical encounter and the degree to which that outcome matches up to their initial expectations of the consultation.[10] A common reason for anger in the doctor-patient relationship is disappointment of expectation.[11]

There have been far fewer surveys of the doctor's perception of the clinical encounter despite most doctors acknowledging that they are influenced by the character of the patient and the patient's family. Those dealing with children are aware that they are influenced by the child's parents and acknowledge that the care is likely to be less good if the parents seem to them difficult, unlikeable, or irritating.[12]

In this survey nearly 80% of doctors responded to a postal questionnaire, and did so at length. That is heartening because, though most doctors treating children try hard, on behalf of the child, to provide optimal treatment regardless of interfering factors, they are far more likely to achieve that even handed approach if they acknowledge that certain parents do make it difficult for them to provide optimal treatment. Moreover, acknowledging that difficulties do arise for doctors, as well as patients, in consultations can be a starting point for postgraduate education, problem solving, and better training.[13]

It is worrying that the response rate from nurses was poor and that so few acknowledged that parents could be difficult or unlikeable and that those qualities might make a child's medical care less good. The limited response from nurses may have resulted from several factors. A minority of senior nurses adopted a discouraging attitude to the questionnaire, which led to poor response and apparent lack of candour from their staff. Other nurses were encouraged to complete the questionnaire by their seniors, but it may be that being less used to research questionnaires, tending to be younger and more junior than the doctors, some find that the only way to cope with difficult families is to pretend that none are difficult or unlikeable. Those concerned with training are more likely to feel that the starting point for better relationships is to acknowledge problems and work out ways of coping with them.

The features which caused the hospital doctors to feel that a parent was difficult or unlikeable will be familiar to most doctors. Several of the characteristics were similar to those that have been said to cause adult patients to seem 'hateful'.[14] Aggressive combative parents were unpopular, but few doctors felt physically threatened by them. In contrast the nurses were worried by the prospect of physical violence and, bearing in mind the lonely responsibilities of many young nurses late at night in hospital, it is an understandable fear.

Parents who harmed their child were mentioned by both doctors and nurses. To the doctors it was usually verbal, emotional cruelty that they resented; none mentioned parents who had physically or sexually abused their children. In contrast many nurses did find parents who had physically abused their children unlikeable. The doctors were conscious also that the parent's negative attitude to their child sabotaged any suggested management regimen.

The fact that so many doctors complained about persons other than a parent accompanying the child to a consultation is worrying. In the last 20 years there has been a steady increase in the number of people accompanying a child to, for instance, an outpatient clinic. Formerly it was nearly always the mother with the child. Now it is commonly both parents and, quite often, a grandparent as well. On other occasions a parent comes with a friend or relative for support. They do so because they are concerned for the child, or because a single parent is apprehensive of the hospital and the consultation and needs a relative or friend for support. Yet most doctors do not find dealing with more than one parent easy. (Even Illingworth, with his considerable wisdom and clinical experience, found grandmothers irritating.[15]) A cynic might argue that the doctor prefers to be in a powerful position and does not like being outnumbered; more likely is simply the problem of knowing with whom to talk when there are two or three people representing the child. Whose eyes does one look at, to whom does one ask the questions?

Child psychiatrists and some other therapists are skilled at group communication and family therapy, but most other doctors dealing with children do not cope well with more than one relative at a time. Clearly those with the skills to deal with groups need to pass on those skills to those of us without them.

Junior doctors were more upset if the child had a condition they did not understand than were the senior doctors. (Perhaps consultants are more accustomed to failing to arrive at a diagnosis.) But three quarters of the consultants perceived the parent as more difficult or unlikeable 'If the child has a condition for which I can offer no definite treatment'. This illustrates one of the ways in which doctors work, particularly at outpatient clinics. The doctor is most comfortable if he or she can perform a particular investigation or prescribe a particular treatment. It is a way of concluding a consultation and a way of making themselves, and hopefully the patient, feel that something definite is being done. That so many doctors, when they cannot provide a diagnosis for the child or offer a specific management regimen, see the parent as difficult or unlikeable is partly explained by that group of parents also tending to be combative and blaming (perhaps because of past disappointments with other consultations). It is unfortunate that many adult patients, and parents of child patients, who have chronic problems or unsolvable symptoms spend much time blaming others, particularly doctors, for their unpleasant symptoms. Doctors, for their part, respond poorly to blame and the patient tends to receive worse treatment. However, it must be acknowledged that some doctors, when they cannot diagnose what is the matter with the child nor suggest a management regimen, transfer the child's problem onto the parent and perceive the parent as being partly responsible—and slightly irritating and unlikeable. Several of the doctors had mentioned, in the first part of the questionnaire, their difficulty in dealing with parents when all they had to offer was sympathy and explanation (because there was no further useful investigation to do and no quick effective treatment). It highlights the need for doctors of all grades to have better education in helping people with chronic disorders and unsolvable problems.

The respondents picked out several factors from 13 general features that tended to make them regard a parent as difficult or unlikeable. The result lent some support to the assumption that families whose race, culture, and socioeconomic status is different from that of the doctor's may be more vulnerable to bias and poor care.[16] However, it should be stressed that few doctors signified any factor as making the parent 'definitely' more difficult or unlikeable. Nearly all the responses were 'slightly'. It is sad that parents from the Indian subcontinent should be mentioned by two thirds of the consultants and nearly half of the juniors. It is even sadder that the reason given by the doctors for that opinion was mainly concerned with communication problems, many of which could be solved by satisfactory translation services. When, in so many of our health districts, a high proportion of child patients are Asian and have parents with limited English, it is scandalous that translator services are so limited. In developed countries such as ours a diagnosis of a child's illness is primarily from the history rather than the examination; young children cannot provide their own history and it is essential for the doctor dealing with them to be able to communicate with a parent. Many of the parents cannot speak English nor organise themselves to arrive at hospital with someone who can translate for them. Too many hospitals have skeleton, voluntary translator services which may not be available even at peak outpatient clinic times, and which are absent when children are admitted as emergencies, usually in the evenings.

Nearly half of all doctors signified 'much less clever' as an unlikeable parental characteristic, usually linking it with the ensuing communication difficulties. The 'much more clever' parents who were difficult, were deemed so usually because of pressing for priority treatment and for more than their share of health service time. Few doctors were adversely influenced by parents who were considerably older or younger themselves. The myth that male paediatricians provide the best service for children who have attractive mothers was not supported (nor was it in the survey of primary care paediatricians in the USA, where a great many maternal characteristics, including safety consciousness, came well ahead of the mother's appearance or nature[12]).

Most doctors, unlike nurses, were prepared to write at length about the features that made parents seem difficult or unlikeable. Several expressed their misgivings, and sometimes guilt, about their prejudices. However, it was good that the doctors acknowledged them, and perhaps we should ask ourselves whether it is realistic to expect to feel that we have to like all our patients and their families. We do need strategies for coping with our own emotions and feelings and, in particular, with those parents who seem to be difficult and unlikeable not only to us but to their spouse, their neighbours, and the rest of society. Most of us feel inadequate when confronted by such a belligerent mother of a violent disruptive child. Perhaps we need to acknowledge that she probably knows that everyone, including the neighbours and doctors, dislike her. There may be ways forward by saying 'I suppose you must feel persecuted as a result of Thomas's behaviour' and by finding if there is anything in life which is not too awful; 'Can you think of *any* good thing Tom does', or in the parents' relationship 'Is there *anything* that you are able to talk about or do together'? Those of us who feel inadequate with belligerent unlikeable parents perhaps should feel grateful for what they do give us, and what they are showing by taking the time and the trouble to bring their child to us for a consultation, even if they are complaining and obstructive and non-complying they have brought their child and themselves to the clinic. Nevertheless most of us will continue to have difficulty finding ways of dealing with our feelings about some parents of child patients. We wish to do the best for the child and know that our feelings, at times, interfere with that. It is likely that child psychiatrists, family therapists, and other colleagues can contribute, during in-service training, to enable all grades of medical staff to achieve better understanding and better approaches to difficult and unlikeable people. The subject should be discussed and not avoided.

I am grateful to all those who cooperated with the questionnaire and, particularly, to the majority who sent back long and thoughtful replies I am grateful to Wendy Pearson and Mandy Jones for their assistance

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Archives of Disease in Childhood 1992; 67: 703–705

Asthma, inhaled corticosteroid treatment, and growth

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Accepted 10 February 1992

Abstract

To evaluate the effects on growth of inhaled corticosteroid treatment (ICT) and of the quality of control of asthma, height velocity was studied in 58 prepubertal children attending a specialist asthma clinic because of chronic asthma that was difficult to control. The height velocity standard deviation (SD) score was maximal when the asthma was well controlled both before (0·01) and after (−0·07) starting ICT. It was least when the asthma was poorly controlled both before (−1·50) and after (−1·55) starting ICT. The effectiveness of control correlated significantly with the height velocity SD score, both before and after ICT was started. No evidence was found that the administration of ICT has an adverse effect on growth.

Inhaled corticosteroid treatment (ICT) has been used to treat moderate to severe asthma since the early 1970s,[1, 2] the two drugs most commonly used in the UK are beclomethasone dipropionate and budesonide. Occasional minor side effects such as oral thrush, dysphonia, and hoarseness have been reported.[1, 3] Adrenal suppression has been observed in patients on ICT, but the dose at which this occurs varies. Some investigators have noted evidence of adrenal suppression in patients on conventional doses of ICT,[4, 5] while others have found adrenal dysfunction only with higher than conventionally recommended doses.[1, 6]

Growth retardation in severe childhood asthma was described long before the introduction of ICT[7–9]; it also occurs as a complication of long term systemic corticosteroid treatment for asthma.[10, 11] The effect of ICT on linear growth, is however, controversial.[1–3, 12–14]

This study evaluated the effects of ICT and the severity of asthma on linear growth in prepubertal children with severe chronic bronchial asthma, many of whom were poorly controlled despite higher than conventionally recommended doses of ICT.

Patients and methods

The growth of 58 children (38 boys and 20 girls) with chronic asthma was followed up for a mean duration of 4·9 years (range 2·6–9·4 years).

The children studied were suffering from recurrent or chronic asthma, which was sufficiently severe to require regular hospital review that included assessment of their growth. Height was measured on the same stadiometer by a small group of nurses who were also responsible for measuring children attending the local growth centre, thus ensuring a standardised technique. Asthma control was assessed by a symptom score based on the frequency, duration, and severity of wheezing and on the number of days per week on which rescue medication (systemic steroids or bronchodilator treatment) was used (table 1). For each category a score of 0–4 was given to produce a maximum of 16 points. A score of 5 or less was classed as good control, 6–10 as moderate control, and greater than 10 as poor control. Each of these children were followed up for a minimum of one year when not receiving ICT and for at least another year when on a continuous ICT.

To avoid pubertal influences, growth was studied in boys until the 11th birthday and in girls up to the 10th birthday. The mean age of entry into the study was 3·5 years for boys and 4·4 years for girls. The mean age of exit from the study was 9 years for boys and 7·5 years for girls.

Each child was treated initially with β_2 receptor stimulants, theophylline, and/or sodium cromoglycate for a mean duration of 1·8 years (range 1–6·5 years). Because of inadequate control of interval symptoms the children were then started on ICT (budesonide or beclomethasone dipropionate). The selection of drug was based on the type of inhalation device which the patient was best able to use: budesonide was generally given by a large spacer (Nebuhaler, Astra) whereas beclomethasone dipropionate was generally given by metered dose inhaler or dry powder inhaler (Rotahaler, Allen and Hanburys).

Table 1 Asthma symptom score

	Score			
	1	*2*	*3*	*4*
Frequency of wheezing in the past 2 months (days)	0–3	4–7	8–14	>14
Typical duration of episodes (hours)	<1	1–6	7–24	>24
Type of treatment required	Inhaled (<4 puffs/day)	Inhaled (≥4 puffs/day)	Nebuliser	Hospital admission
Rescue medication in the past 2 months (days)	<4	4–7	8–14	>14

To achieve rapid control of the asthma ICT was usually started at a dose of 400 µg per day that was then adjusted (usually downwards) at regular intervals depending on the response to treatment. In most patients satisfactory control was attained rapidly on ICT given in a dose of 400 µg or less per day, and the patient was discharged from further review. The patients in the present study are those in whom satisfactory control of symptoms was harder to achieve, who commonly required higher doses of ICT, and who therefore required long term review. In the patients studied the median dose of ICT was 800 µg (range 200–1600 µg); treatment with sodium cromoglycate was suspended once ICT was commenced. The children were then followed up for a mean duration of 2·7 years (range 1–5·1 years).

Height velocity was calculated and expressed as height velocity standard deviation (SD) scores according to age using the formula:

$$\text{Height velocity SD score} = \frac{\text{Height velocity} - \text{mean height velocity for age}}{\text{SD of height velocity for age}}$$

After calculating the height velocity SD score the values were centralised on the point at which ICT was commenced and, because of the non-normal distribution of the values, geometric means were calculated for each patient before and after starting ICT. Analysis of variance was used to evaluate the effect on growth of sex and asthma control before and after the administration of ICT. Correlation coefficients were used to evaluate the relationships between asthma control, sex, and height velocity SD score before and after starting ICT.

Results

The 58 children had a mean height velocity throughout the period of observation of −0·54 (range −4·20 to +2·90). The rate of growth for girls was less than that of the boys though the difference between the means was not statistically significant (table 2). From tables 3 and 4 it is apparent that subjects whose asthma was well controlled grew well whereas those subjects whose asthma was badly controlled grew poorly, regardless of whether or not they were receiving ICT. Height velocity SD score correlated negatively with control of asthma both before and after commencing ICT (table 5) but not with the dosage of ICT used.

*Table 2 Mean height velocity SD score of the 58 children studied. Results are mean (SE)**

	Before ICT	*After ICT*
Boys (n=38)	−0·42 (0·19)	−0 53 (0 19)
Girls (n=20)	−0 76 (0 22)	−0 70 (0·24)
All (n=58)	−0 51 (0 14)	−0 59 (0 14)

*There was no significant difference between the means before and after ICT

Table 3 Effect of asthma control on height velocity SD score before ICT was started

Control	*Mean (SE)*	*95% Confidence interval*
Good	0·01 (0·14)	−0 27 to 0 30
Moderate	−0·83 (0·23)	−1 33 to −0 34
Poor	−1 50 (0·39)	−2 37 to −0·62

Significance of difference between means good *v* poor, *t*=3 64, p=0 003, good *v* moderate, *t*=3 11, p=0·004, and moderate *v* poor, *t*=1 45, NS

Table 4 Effect of asthma control on height velocity SD score after ICT was started

Control	*Mean (SE)*	*95% Confidence interval*
Good	−0 07 (0·24)	−0·60 to 0 45
Moderate	−0·49 (0·17)	−0 85 to −0·13
Poor	−1·55 (0·31)	−2 25 to −0 85

Significance of difference between means· good *v* poor, *t*=2·92, p=0·009, good *v* moderate, *t*=1 39, NS, and moderate *v* poor, *t*=3 67, p=0·001.

Table 5 Correlation coefficients between sex, ICT dose, asthma control, and height velocity SD score before and after starting ICT

	Control		*Height velocity SD score*	
	Before	*After*	*Before*	*After*
Sex:				
r	−0·080	−0·197	−0·166	−0 160
p	0·278	0·071	0·108	0 107
Dose:				
r		0·160		−0 199
p		0 117		0 69
Control.				
r			−0·54	−0·458
p			0·000	0·000

The height velocities of the 16 children on whom we had growth data for more than two years both before and after starting ICT were considered separately on a year by year basis; there was no change in height velocity after starting ICT.

Discussion

The use of inhaled steroids is firmly established as one of the mainstays in the maintenance treatment of children with moderate and severe asthma.[1-3] The currently accepted indication for long term use of ICT is the presence of chronic asthma that is not adequately controlled by non-steroidal drugs. In most children adequate control of asthma can be obtained with doses between 100 and 600 µg per day.[15] The therapeutic effects of ICT are, however, dose dependent[16] and it may occasionally become necessary, as in the majority of children in this study, to increase the dosage to achieve optimum control of the asthma.

Although Littlewood *et al* concluded that ICT produced growth impairment in asthmatic children,[13] many of their patients were of an age when pubertal changes would be expected to be influencing growth. Balfour-Lynn has shown that asthma is associated with a relative deceleration of growth in later childhood leading to delayed puberty.[12] In our study pubertal influences were avoided by studying boys only until the 11th birthday and girls until the 10th birthday. Objective measurements on the pubertal status of the children were not made, though the ages at exit (mean 9 years for boys and 7·5 years for girls) would make it unlikely that pubertal changes played a significant part.

The 58 children in this study, whose asthma was frequently poorly controlled, tended to show relative growth impairment both before and after they were commenced on ICT, a previously observed phenomenon.[17]

Of the possible influences on growth that we studied, the only factor with a significant effect was the quality of control of the asthma. The linear growth of children with poorly controlled asthma was significantly slower than in those whose asthma was well controlled, a finding which was observed both before and after starting ICT (tables 3 and 4). The dose of ICT did not correlate with height velocity SD score (table 5) and although girls showed slightly more growth impairment than boys, the difference was not significant.

In this study it was apparent that whereas the control of the asthma had a major effect on growth, ICT had no such effect. This finding is in keeping with the observation long before ICT was introduced that childhood asthma is associated with growth impairment,[7–9] a finding which has been related to both the severity of the asthma[18] and to the existence of the atopic state.[17]

We have therefore been unable to demonstrate any adverse effect of ICT on growth; when growth impairment occurs in an asthmatic child this is more likely to reflect poor asthma control than the administration of ICT.

We thank Daphne Russell for helpful statistical advice and Dr Peter Smail for advice on the calculation of height velocity SD scores

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Archives of Disease in Childhood 1992; 67: 706–708

Mononuclear cell subsets and coronary artery lesions in Kawasaki disease

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Accepted 14 January 1992

Abstract

The peripheral blood mononuclear cell subsets in patients with Kawasaki disease and coronary artery lesions were investigated. Of the 106 patients 14 had lesions. Patients with Kawasaki disease and coronary artery lesions were found to have increased counts of CD14+ macrophages/monocytes compared with those of patients with Kawasaki disease without lesions. The absolute counts of CD14+ macrophages/monocytes form an important parameter to determine the severity of vascular damage during acute Kawasaki disease.

The immunological abnormalities observed in patients with Kawasaki disease are related to hyperreactive responses in immunocompetent cells because of the increased cytokine production[1–3] and expression of activated antigens on their cell surface.[4 5] Several studies have reported on numerical changes of immunocompetent cells in patients with Kawasaki disease.[6] However, there have been no reports concerning changes in patients with Kawasaki disease and coronary artery lesions as there are few patients with these lesions and Kawasaki disease. We investigated the peripheral blood mononuclear cell subsets in patients with Kawasaki disease and coronary artery lesions and compared the subsets counts with those of patients without lesions.

Patients and methods

Inclusion in this study depended on patients meeting the diagnostic criteria for Kawasaki disease. Sixty five boys and 41 girls were included; they were aged 1–68 months (mean 22 months). The day of onset of fever was recognised as the first day of illness. Blood samples were taken for analysis of peripheral blood mononuclear cell subsets between the third to the ninth days after onset of illness (mean (SD) 5·8 (1·6) days) before treatment by intravenous gammaglobulin and aspirin or aspirin alone. Patients received aspirin 30 mg/kg/day in three divided doses up until the 30th day after the onset of fever. Of the 106 patients with Kawasaki disease, 60 received the same course of aspirin and in addition received an infusion of intravenous gammaglobulin (Venilon, Teijin Limited, Tokyo) in a 5% solution at a daily dosage of 200 mg/kg for five consecutive days. Sixty seven of the 106 patients with Kawasaki disease were sampled for peripheral blood mononuclear cell subsets on the ninth to 15th days (mean (SD) 11·5 (2·0) days) of illness, after treatment by intravenous gammaglobulin or during treatment by aspirin alone. Thirty six of the 67 patients with Kawasaki disease received aspirin and an infusion of intravenous gammaglobulin and the others received aspirin alone. In addition, 68 patients were examined for peripheral blood mononuclear cell subsets on the 20th to the 68th days (mean (SD) 33·9 (19·9) days) of illness during the convalescent stage. Two dimensional echocardiography was used to detect the presence of coronary artery lesions twice a week after admission. In accordance with the cardiovascular lesion diagnostic criteria in Kawasaki disease of the Research Committee on Kawasaki Disease coronary arteries with diameters of 4 mm or greater were regarded as exhibiting lesions.[7] The control subjects were 22 healthy children aged 4–67 months (mean 26 months).

Using a method previously described,[4 5] the percentage of the peripheral blood mononuclear cell subsets among mononuclear cells was assayed. The percentages of mononuclear cell subsets were assayed with a fluorescence activated cell sorter (FACS IV, Becton Dickson Immunocytometry Systems). For fluorescence procedures fluorescein isothiocyanate conjugated monoclonal antibodies used were as follows: CD3/Leu 4, CD4/Leu 3a, CD8/Leu 2a, CD57/Leu 7 (a natural killer cell and a part of T cell markers), CD19/Leu 12, or CD14/Leu M3 (Becton Dickinson Monoclonal Center). The mononuclear cell population was gated according to orthogonal scatter and forward scatter. Next, to exclude macrophages/monocytes from the analysis, the lymphocyte population was gated according to orthogonal scatter and forward scatter. From the ratio of peripheral blood mononuclear cells to white cell counts, the absolute counts of mononuclear cell subsets were calculated. Statistical analyses were performed using the Student's *t* test.

Results

During a 30 day period after the onset of the disease, 14 patients were shown to have coronary artery lesions. Eight of these 14 patients received aspirin and an infusion of intravenous gammaglobulin and the others received aspirin alone.

Table 1 shows the absolute counts of white cells, mononuclear cells, lymphocytes, and mononuclear cell subsets during the acute stage before treatment and during the convalescent stage of Kawasaki disease together with control subjects. The absolute counts of CD14+ macrophages/monocytes and CD19+ B cells found in patients with Kawasaki disease were increased

Table 1 Absolute counts of white cells, mononuclear cells, lymphocytes, and mononuclear cell subsets during the acute stage before treatment and during the convalescent stage of Kawasaki disease and of control subjects All results for cell counts are expressed as ×10⁹/l and mean (SEM)

	Acute stage	*Coronary artery lesions*		*Convalescent stage*	*Controls subjects*
	(n=106)	*With (n=14)*	*Without (n=92)*	*(n=68)*	*(n=22)*
Mean (SD) day sample taken after onset of fever	5·8 (1·6)	6·1 (1·4)	5·7 (1·7)	33·9 (19·9)	
White cells	15·59 (0·47)†	16·94 (1·07)	15·38 (0·52)	8·56 (0·29)	8·41 (0·39)
Mononuclear cells	4·58 (0·21)	4·86 (0·79)	4·54 (0·21)	5·27 (0·20)	4·86 (0·25)
CD14+ macrophages/monocytes	0·52 (0·04)†	1·02 (0·15)†‡	0·45 (0·03)	0·25 (0·02)	0·18 (0·02)
Lymphocytes	4·06 (0·20)	3·85 (0·69)	4·09 (0·20)	4·89 (0·19)	4·68 (0·25)
Lymphocyte subsets:					
CD3+ T cell	2·38 (0·14)	2·25 (0·43)	2·39 (0·14)	3·16 (0·14)	2·98 (0·24)
CD4+ T cell	1·81 (0·11)*	1·88 (0·41)	1·80 (0·12)	2·27 (0·11)	2·33 (0·19)
CD8+ T cell	0·78 (0·04)*	0·81 (0·18)	0·78 (0·04)	1·14 (0·06)	0·94 (0·06)
CD57+ cell	0·24 (0·02)*	0·30 (0·09)	0·23 (0·02)	0·58 (0·07)	0·35 (0·06)
CD19+ B cell	1·23 (0·09)*	1·78 (0·48)	1·18 (0·09)	1·00 (0·06)	0·94 (0·10)

*Significant at p<0·05 *v* control subjects, †significant at p<0·01 *v* control subjects; ‡significant at p<0·01 *v* Kawasaki disease without lesions.

during the acute stage preceding treatment compared with those found in control subjects (p<0·01 and p<0·05, respectively). The absolute counts of CD4+ and CD8+ T cells and CD57+ cells found in patients with Kawasaki disease decreased during the acute stage preceding treatment compared with those found in control subjects (p<0·05). These increased absolute counts of CD14+ macrophages/monocytes and CD19+ B cells and decreased absolute counts of CD4+ and CD8+ T cells, and CD57+ cells in patients with Kawasaki disease were seen to be within the normal range during the convalescent stage.

The absolute counts of CD14+ macrophages/monocytes in patients with coronary artery lesions were higher than those of patients without lesions during the acute stage before treatment (p<0·01). There were no significant differences in the absolute counts of CD3+, CD4+ and CD8+ T cells, CD57+ cells, and CD19+ B cells in patients with Kawasaki disease with and without lesions.

Eleven of the 14 patients with Kawasaki disease and lesions were examined for peripheral blood mononuclear cell subsets after treatment by intravenous gammaglobulin (n=6) or during treatment by aspirin alone (n=5). Table 2 shows the absolute counts of white cells and CD14+ marcophages/monocytes of patients with and without lesions after treatment by intravenous gammaglobulin or aspirin alone during the acute stage. The absolute counts of CD14+ macrophages/monocytes found in patients with coronary artery lesions were high during the acute stage after treatment by intravenous gammaglobulin or aspirin alone compared with those found in control subjects (p<0·02). Patients with Kawasaki disease without lesions, treated with aspirin alone, had high absolute counts of CD14+ macrophages/monocytes compared with control subjects and those treated with intravenous gammaglobulin (p<0·01). There was no significant difference between the absolute counts of CD14+ macrophages/monocytes of patients without lesions treated with intravenous gammaglobulin and of control subjects.

Discussion

Treatment with intravenous gammaglobulin has been reported to be effective in reducing the incidence of coronary artery lesions in Kawasaki disease.[8] Before the routine application of this treatment lesions developed in approximately 15% of patients with Kawasaki disease,[9] while recently its incidence has decreased. Our study represents the first report on the determination of the numerical changes of immunocompetent cells in patients with Kawasaki disease and coronary artery lesions. Although several studies have been reported on the numerical changes of immunocompetent cells in patients with acute Kawasaki disease, those previous reports were based on the analysis of peripheral blood lymphocyte subsets.[6] Here we analysed the peripheral blood mononuclear cell subsets including macrophages/monocytes in patients with Kawasaki disease with and without lesions.

The purpose of this study was to compare peripheral blood mononuclear cell subsets in patients with Kawasaki disease with and without coronary artery lesions, although we did not

Table 2 Absolute counts of white cells and CD14+ macrophages/monocytes of patients with Kawasaki disease with and without coronary artery lesions after treatment by intravenous gammaglobulin (IVGG) or aspirin alone during the acute stage

	No of patients	*Mean (SD) day of onset of fever*	*Mean (SEM) white cells (×10⁹/l)*	*Mean (SEM) CD14+ macrophages/monocytes (×10⁹/l)*
With coronary artery lesions	11	11·5 (2·8)	14·34 (2·30)	0·66 (0·16)†
Treated with aspirin	5	11·2 (3·0)	11·01 (1·82)	0·51 (0·20)
Treated with IVGG	6	11·7 (2·5)	16·73 (3·95)	0·79 (0·25)
Without coronary artery lesions				
Treated with aspirin	26	11·5 (1·6)	10·72 (0·61)*	0·35 (0·04)‡
Treated with IVGG	30	11·7 (2·1)	10·37 (0·75)	0·23 (0·02)

*Significant at p<0·05 *v* control subjects (table 1), †significant at p<0·02 *v* control subjects (table 1), ‡significant at p<0·01 *v* control subjects (table 1) and at p<0·05 *v* treated with IVGG include febrile controls in the present study. Patients with Kawasaki disease and lesions were found to have increased counts of CD14+ macrophages/monocytes compared with those of patients without lesions during the acute stage before and after treatment by intravenous gammaglobulin or aspirin alone. The absolute counts of CD14+ macrophages/monocytes in patients without lesions after treatment by intravenous gammaglobulin were lower than those in similar cases treated by aspirin alone. This result supports our previous finding that intravenous gammaglobulin treatment was effective for Kawasaki disease by reducing peripheral blood macrophages/monocytes.[10] However, the absolute counts of CD14+ macrophages/monocytes found in patients with lesions were high during the acute stage after treatment by intravenous gammaglobulin compared with those found in control subjects. Our patients received intravenous gammaglobulin at a daily dosage of 200 mg/kg for five consecutive days as the Research Committee on Kawasaki Disease recommends a total dose of 1·0 g/kg.[11] Our results suggest that immunological activation in these patients persists after treatment with intravenous gammaglobulin and that higher doses may be needed. Further studies are needed in this area.

The macrophage/monocyte has been recognised as a tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) producing cell in inflammatory and immunological reactions. It has been reported that the increased serum concentrations of TNF-α[2] and IL-6[3] and secretion of IL-1 from mononuclear cells[1] are more evident in patients with Kawasaki disease and coronary artery lesions than in patients without lesions during the acute stage. Our results suggest that the absolute counts of CD14+ macrophages/monocytes, together with these cytokines, form an important parameter to determine the severity of vascular damage during acute Kawasaki disease. Our results further suggest that the main characteristics of the pathogenesis of Kawasaki disease are increased numbers of peripheral blood macrophages/monocytes with the secretion of monokines by these activated cells. These immune responses develop more vigorously in patients with Kawasaki disease and coronary artery lesions.

The authors wish to thank Mr S Kuge for technical assistance This work was supported by a research grant (from 1983 to 1991) for the study of Kawasaki disease from the Ministry of Health and Welfare, Japan.

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Archives of Disease in Childhood 1992; 67: 709–711

Tartrazine in atopic eczema

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Accepted 7 February 1992

Abstract

Multiple double blind placebo controlled challenges with tartrazine 50 mg (three challenges) and glucose placebo (three challenges) were performed in 12 children with atopic eczema aged 1 to 6 years. The children were selected on the basis of severity (regular clinic attenders) and a parental history that tartrazine provoked worsening of the eczema. In only one patient did the three tartrazine challenge periods correspond with the highest symptom scores or the highest physician observer scores, and the probability of this occurring by chance in one or more patients out of 12 was 0·46. In this sample we were unable to confirm intolerance to tartrazine in 11 out of 12 patients.

Tartrazine and other artificial food colourings have been reported to provoke asthma[1] [2] and urticaria[3] in susceptible individuals. Van Bever *et al* reported adverse reactions in all of six children with severe atopic eczema challenged with food additives, including two to tartrazine.[4] However, the severity of the reaction was not reported, and the reactions were all of an immediate skin flare type as the observation period of four hours did not allow for the detection of late reactions.

Day to day fluctuation in disease severity, which is a notable though unexplained feature of atopic eczema, and difficulty in objectively quantifying the disease, greatly hinder the interpretation of challenge tests. This is in contrast to other atopic disorders, where an endpoint (for example >25% fall in forced expiratory volume in one second) is more easily defined. Thus, challenge tests in which a single dose of food additive is compared with a single dose of placebo may give a positive result (that is worsening of eczema) in 50% of trials by chance alone. To investigate the effect of tartrazine on atopic eczema, we have therefore used multiple double blind placebo controlled challenges to increase the specificity of the test.

Patients and methods

All patients were attending the University Department of Child Health for treatment of atopic eczema, and all fulfilled the diagnostic criteria of Hanifin and Rajka.[5] There was no age limit for entry, but the children had to be able to drink from a straw. Thirty three consecutive patients with atopic eczema severe enough to require outpatient visits every three months were invited to participate in the study. Twenty three were already on a diet, supervised by a dietitian, which excluded tartrazine and other artificial colours and preservatives because of parental reports of intolerance to tartrazine and other additives. Of these 23, the parents of 16 declined because of fear that tartrazine would exacerbate the child's condition. Ten were started on such a diet, under the supervision of a dietitian, for the purposes of this study. Of these 10, four were excluded from the study because their parents considered that there had been no benefit from the diet. Thus 13 patients (nine boys, four girls; median age 3·8 years; range 1·9–6·9 years) entered the study. The median duration of eczema in these patients was 33 months (range 20–80 months). Seven patients were on an otherwise normal diet, five were excluding one or two foods believed to cause deterioration in their eczema, and one was on a trial of a few food diet. All patients were using topical corticosteroids. Eight used topical hydrocortisone (mildly potent, British National Formulary[6] (BNF) category IV), three used moderately potent (BNF category III) topical steroids, and two used potent (BNF category II) topical corticosteroids. The study was approved by the North Manchester Health Authority ethical committee and informed consent was obtained in each case.

The study period comprised three placebo and three active weeks in random order. There are 20 (6!/3!3!) possible permutations of three placebo and three tartrazine weeks. The regimen for each patient was randomised at entry by the pharmacist drawing a sealed envelope from a shuffled pack containing equal numbers of each permutation. Six gelatine capsules, each containing either tartrazine 50 mg or glucose placebo 50 mg, were supplied in opaque glass bottles numbered corresponding to the order of administration. On the first day of each week, between 8·30 and 11 am the patient attended the ward. Each patient attended at the same time each week. The contents of the appropriate capsule were dissolved in pure orange juice and administered by a nurse to the patient, who drank the juice through a straw from a sealed opaque plastic cup.

The percentage surface area affected by eczema was assessed using a chart similar to one used for recording the surface area of thermal injuries (table 1), and the severity of erythema by a numerical scale from 1 (mild) to 5 (severe). An overall combined severity score was obtained by multiplying the percentage surface area by the erythema score. The assessment was performed by a single observer (JD), immediately before the administration of the

Table 1 Assessment of eczema extent

	Demarcation	*% Surface area*
Face+scalp	Anteriorly, angle of jaw; posteriorly, hairline	14
Neck	Anteriorly, jaw to upper border clavicles, posteriorly, hairline to line between acromion tips	4
Right arm	Acromion tip to two finger breadths above ulnar head	7
Left arm	Acromion tip to two finger breadths above ulnar head	7
Right hand	Distal to two finger breadths above ulnar head	4
Left hand	Distal to two finger breadths above ulnar head	4
Trunk	Clavicles to line between ASIS	10
Back	From line between acromion tips to line between ASIS	12
Pelvis	From line between ASIS to pubic tubercles	4
Buttocks	From line between ASIS to gluteal folds	6
Right leg	From line joining ASIS and pubic tubercles anteriorly and from gluteal folds posteriorly to three finger breadths above medial malleolus of tibia	10
Left leg	From line joining ASIS and pubic tubercles anteriorly and from gluteal folds posteriorly to three finger breadths above medial malleolus of tibia	10
Right foot	Area distal to three finger breadths above medial malleolus of tibia	4
Left foot	Area distal to three finger breadths above medial malleolus of tibia	4

ASIS=anterior superior iliac spines

tartrazine or placebo, and again 24 to 48 hours later, and the change in score (increase or decrease) was used as the parameter for analysis.

The parents were asked to keep a record of symptoms—severity of itch, skin redness, night time disturbance, urticaria, itchy or runny nose, wheeze, and behaviour problems—on a scale of zero (no problem) to 10 (very severe), each day for seven days after the administration of the capsule. For each week, a mean daily score for each symptom was calculated. A combined eczema symptom score was derived by summing the mean daily scores for itch, redness, and nocturnal disturbance with a maximum possible score of 30. A positive challenge was defined as one in which the three tartrazine weeks corresponded either to the three with the highest symptom scores or to the three with the greatest increase in severity score, the probability of such a correspondence being 0·05 for each comparison.

Data were analysed for results on individual subjects to determine the frequency of positive challenges, and the tartrazine and placebo weeks were compared for the group as a whole.

Results

Challenges were abandoned in one patient who moved from the area after the second challenge. The data from the remaining 12 patients were analysed.

Table 2 Details of eczema symptom and severity scores

Patient	*Mean daily symptom scores*		*Change in severity score after capsule*	
	Tartrazine	*Placebo*	*Tartrazine*	*Placebo*
A	2, 5·1, 10	3·3, 5·4, 9·7	0, 0, 0	0, 0, 0
B	15·1, 15·4, 3·7	11·3, 14·3, 16	0, +68, −33	−38, +12, +2
C	23·7, 23·7, 25·4	23·3, 25·4, 25·9	+25, +27, 0	+2, −2, −18
D	7, 4·3, 9	6·4, 5·4, 8·1	+6, +3, −1·5	+2·5, +1, −8·5
E	9·7, *, 17·9	12·9, 6·6, 10·7	0, 0, +12	0, −108, +28
F	10·4, 6·9, 4·9	5·9, 4·7, 5·7	0, −23·5, 0	−12, 0, +16
G	0·9, 2·1, 0	0·3, 7·4, 1·9	0, 0, −10·5	0, −3, 0
H	17·1, 1[illegible], 1[illegible]	*, 14·1, 18·3	+63, +73, −4	0, +73, +62
I	9·3, 15·3, [illegible]4·9	4·6, 4·3, 11·4	−5, 0, −16	0, 0, −16
J	9, 7·3, 10·[illegible]	7, 10·9, 8·9	0, 0, −21	0, −26, +2
K	11, 13·1, 1[illegible]	11·9, 11·6, 6·4	0, +14, −28	−4, −4, 0
L	10·9, 10·9, [illegible]·9	9·3, 9·4, 9·3	+32, +21, +3	0, +2, −14

*Data not available (see text)

INDIVIDUAL DATA

Eczema

Two of the 12 patients who completed the study period lost their diary cards for one week, but there were sufficient symptom score data from the other five weeks to exclude a reproducible reaction to tartrazine and these patients were regarded as negative challenges (table 2).

In one of the 12 patients (patient L) the three tartrazine challenges corresponded with the three weeks which had the highest symptom score and also with the three weeks which had the greatest increase in observed eczema severity. There was no such correspondence in either symptom or disease severity score in any of the other 11 patients. According to the binomial theorem, in N independent trials, where the probability of an event occurring in each trial is p, the probability that the event will be observed in at least k trials is given by[7]:

$$1-\sum_{0}^{k-1}\frac{N!p^{x}(1-p)^{N-x}}{x!(N-x)!}$$

Given that the probability of the three worst weeks of six corresponding to the three tartrazine weeks by chance in a single patient is 0·05, the probability of this occurring in one or more patients out of 12 is 0·46.

Other symptoms

In one patient (G) the three worst weeks for wheeze and the three worst for rhinitis corresponded to the three tartrazine weeks. No other patient showed positive challenges for these symptoms. Three patients each had a single episode of urticaria, each occurring during a tartrazine week. No patient showed behavioural changes related to tartrazine administration.

GROUP DATA (TABLE 3)

Eczema

The total daily eczema symptom scores for the three tartrazine weeks were combined and compared with those for the placebo weeks in each of the 10 patients for whom full data was available (parents' data were missing in two subjects). Although the median score for the tartrazine weeks (216) was higher than that for the placebo weeks (154), the difference was not significant (p>0·1, Wilcoxon signed rank test). The changes in eczema severity score were summed for the three tartrazine weeks and compared with the summed changes in the placebo weeks for all 12 of the patients. Again, although the median change in score was higher in the tartrazine weeks (+4) than in the placebo weeks (−6), the difference was not significant (p>0·1, Wilcoxon signed rank test).

Other symptoms

Similarly, the total symptom scores for wheeze, rhinitis, and behaviour for the three tartrazine weeks were compared with those for the placebo weeks in each of the 10 patients for whom full data were available. No significant difference

Table 3 Group results combining three tartrazine and three placebo weeks

Patient	*Mean daily symptom scores for*								*Mean change in severity‡ 24 hours after challenge given*	
	*Eczema**		*Rhinitis†*		*Wheeze†*		*Behaviour†*			
	Tartrazine	*Placebo*	*Tartrazine*	*Placebo*	*Tartrazine*	*Placebo*	*Tartrazine*	*Placebo*	*Tartrazine*	*Placebo*
A	5·7	6·1	0·3	1·0	0	0	1·3	1·7	0	0
B	14·8	13·9	0·2	0·5	0	0	0	0	+12	−8
C	24·3	24·9	5·5	5·0	7·6	7·3	6·0	5·6	+8	+4
D	7·4	6·7	0	0	0	0	0	0	+2	−2
E	NA	NA	NA	NA	NA	NA	NA	NA	+4	−27
F	7·4	5·4	1·4	0·9	0	0	0·3	0	−8	+1
G	1·0	3·2	0	0·3	0·2	0·3	0·2	0·4	−4	−1
H	NA	NA	NA	NA	NA	NA	NA	NA	+44	+45
I	13·1	6·8	2·7	2·0	3·0	2·0	3·1	1·4	−7	−5
J	8·8	8·0	0	0	0	1·4	3·1	2·7	−7	−8
K	11·7	10·0	4·4	3·6	3·5	3·4	2·1	2·1	−5	−3
L	12·2	9·3	3·0	3·4	0	0	3·2	4·0	+18	−4

*Maximum score 30, †maximum score 10 ‡ Plus sign denotes deterioration, minus sign denotes improvement NA=data not available

was found for any of these symptoms ($p>0\cdot 1$, Wilcoxon signed rank test).

Discussion

This project was designed to try to overcome the difficulties encountered in studying a disease which is difficult to quantify objectively and which is characterised by unpredictable fluctuation in severity. Our method can be assumed to have a 'false positive' rate of 5%, and so cannot be used to screen a population with a very low prevalence of additive intolerance. One problem in the interpretation of this study is that the improvement obtained on the artificial colouring and preservative free diet could in theory have been due to the exclusion of an additive other than tartrazine, notwithstanding parental observation of intolerance to tartrazine. To investigate the possibility of intolerance to other additives would have been impractical. For example, to have studied only 10 other additives would have required weekly attendance at hospital for a further 60 weeks. We chose to investigate a single azo dye, tartrazine, because this commonly used food colouring is one of those most frequently implicated in adverse reactions, and because the parents of the subjects in the study believed their child to be intolerant to tartrazine. There is an hypothetical argument that as the mechanism of tartrazine intolerance is unknown, the timing of an adverse reaction cannot be predicted and might appear towards the end of an 'active' week or even in the next week. To detect such delayed reactions would require a wash-out period of arbitrary duration after each active week to prevent contamination of 'placebo' weeks. Against this argument is the observation from double blind placebo controlled challenge studies that adverse reactions to tartrazine were almost immediate and occurred within three to four hours after ingestion.[3 8 9]

In only one patient of the 12 studied was there a clear correspondence between tartrazine administration and worsening of eczema, as assessed both by symptoms and clinical examination, but, as explained above, this would have been expected by chance alone. A second patient had wheeze and rhinitis symptoms which correponded to tartrazine weeks. We also sought, but failed to find, evidence of a more subtle effect of tartrazine administration, not detectable in an individual subject but evident in the group as a whole.

The mechanism by which tartrazine might cause deterioration in eczema remains obscure. Our one patient who appeared to react consistently showed an objective worsening in her skin when examined clinically, approximately 24 hours after each dose of tartrazine and lasting for three to four days. Her parents did not notice any urticarial lesions.

Reluctance to participate in the study for fear of adverse reaction was a problem when recruiting patients, in contrast to the ease we have experienced in finding patients willing to try new possibly beneficial treatments. It is possible that, as with behavioural problems attributed to tartrazine,[10] parental anxiety about the adverse effects of tartrazine in atopic eczema may be disproportionate.

We would like to thank Mr J Lockwood, principal pharmacist, Booth Hall Children's Hospital, for preparing the capsules and randomising the patients, and the nursing staff of Ward 4 for their help JD was supported by the National Eczema Society

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Archives of Disease in Childhood 1992; 67: 712–716

Dysmorphic features in offspring of alcoholic mothers

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Abstract

The frequencies of 60 minor physical anomalies and various craniofacial measurements in 52 children with alcohol exposure of various durations in utero were determined and compared with 48 non-exposed healthy children at a mean age of 27 months. Compared with non-exposed children a significantly higher total minor physical anomaly count was observed in those children exposed prenatally to alcohol throughout pregnancy. Binge drinking was not associated with an increased minor physical anomaly count. During the first year of life facial features were judged according to subjective impression: 10 children had typical facial features of fetal alcohol syndrome (FAS) and 19 children were judged to have possible fetal alcohol effects on their face. Only six of them fulfilled the strict craniofacial criteria for diagnosis of FAS at the age of 27 months. Our results stress the importance of recognising also the subtle dysmorphic facial features associated with prenatal alcohol exposure: 22 of 29 (76%) of exposed children judged to have typical or possible features of FAS during the first year showed signs of central nervous system dysfunction at the age of 27 months.

When Jones and his colleagues reported the association between exposure to alcohol in utero and aberrant morphogenesis, the most frequent minor physical anomalies observed were short palpebral fissure, altered palmar crease patterns, maxillary hypoplasia, and epicanthus.[1 2] Since then a considerable variety of minor anomalies has been reported.[3–8] When the Fetal Alcohol Study Group of the Research Society on Alcoholism (RSA) set the minimum criteria for the diagnosis of fetal alcohol syndrome (FAS) only minor physical anomalies of the facial area were included.[9] In addition to growth retardation and dysfunction of the central nervous system, a diagnosis of FAS requires at least two of the following three craniofacial signs to be present: (i) microcephaly, (ii) microophthalmia and/or short palpebral fissure, and (iii) hypoplastic philtrum with thin upper lip and flattening of the maxillary area.

In addition to the widely used definition of the RSA, Majewski[10] and Vitez *et al*[11] have presented two different semiquantitative scoring systems for the probability and severity of FAS, both of which include the RSA criteria. Majewski included 23 minor and major anomalies in his 29 item scoring system and Vitez *et al* 45 malformations in their 51 item scoring system.

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Accepted 21 February 1992

The first aim of the present study was to analyse the occurrence of minor physical anomalies in children exposed to alcohol in utero and to compare these with non-exposed children in order to see whether the duration of alcohol exposure was associated with the amount or type of minor physical anomaly. The second aim was to decide whether the subjective assessment of facial features during the first year of life suggestive of fetal alcohol exposure can be affirmed by an independent examination during the third year of life. The third aim was to study whether judgment based on a subjective impression can be of clinical value in diagnosing children with possible fetal alcohol effects.

Subjects

Eighty two children exposed to alcohol in utero were followed up prospectively at the Children's Castle Hospital, Helsinki. The mothers had entered the study in their second trimester and were followed up at two to four week intervals at a special outpatient clinic for pregnant women at the Helsinki University Central Hospital.[12] At each visit the mothers were informed of the harmful effects of fetal alcohol exposure and were encouraged to stop their drinking. The mothers' reports on their drinking, use of drugs, and smoking were recorded for each interval between visits. Alcohol consumption was assessed according to Rosett *et al* as heavy if it exceeded 140 g per week or 630 g per month.[13] Children were divided into three groups according to the recorded data. Group I consisted of children exposed to heavy alcohol consumption during the first trimester only (n=29). Group II consisted of children exposed to heavy alcohol consumption during the first and second trimesters (n=27). Group III consisted of children exposed to heavy alcohol consumption throughout pregnancy (n=26). Eight mothers reported mainly moderate (24–140 g per week) but regular alcohol consumption during their first trimester, and they were included in group I. The pattern of drinking was classified as either binge drinking (five or more drinks on one occasion) or not.

After birth the children were systematically followed up at the Children's Castle Hospital, the examiners being unaware of exposure status.[14 15] At the fifth assessment at a mean age of 27 months the developmental levels of 60 (73%) exposed children were assessed by a psychologist and a speech therapist.[16] Fifty two (63%) of these children underwent a thorough assessment of their dysmorphic features, which were recorded by one of the authors (EG); 51 of them were seen at least once during their first year of life.

The non-exposed group was composed of 48 children who were exposed only to vitamins, iron substitution, and non-teratogenic antibiotics. Sixteen children were born to abstinent mothers who had been checked regularly during pregnancy at the outpatient clinic for alcohol consuming pregnant women.[17] Thirty two children were born to abstinent low social class women collected from a large prospective population based study on alcohol consumption during pregnancy.[18]

Methods

During the first year of life the facial features of the child were subjectively assessed as normal, possible fetal alcohol effects (FAE face), typical FAS face, and abnormal not resembling FAS by one of us (IA-R).

At a mean age of 27 months (24–36 months), the minor physical anomalies of the children were systematically recorded according to a checklist of 60 minor physical anomalies (table 1) by one of us (EG). The checklist was based on the dysmorphology patterns presented by Smith[19] and modified according to the reports on dysmorphic features in children exposed to alcohol in utero.[1–4 11] Fingertip patterns were classified according to Penrose.[20] Three or more arches was regarded as abnormal, as in a previous Finnish study.[21]

The frequencies of all the features given in table 1 were computed for the exposed and non-exposed groups. According to Marden *et al*[22] and Leppig *et al*,[23] only those features found in less than 5% of the 48 non-exposed children were regarded as minor physical anomalies in this study (because of the small number of non-exposed children the limit was changed from the original 4% to 5%). Of those features omitted from further analysis dysmorphic ears (three of non-exposed and nine of exposed children, $p<0{\cdot}05$) and hypoplastic philtrum (three of non-exposed and nine of exposed children, $p<0{\cdot}05$) were seen significantly more often in the exposed children. For the analysis of data the number of minor physical anomalies in each child was used as the minor physical anomaly score.

Table 1 Checklist of 60 minor anomalies.+Those observed in more than 4% of the non-exposed children

Abnormal head shape
Prominent forehead*
Abnormal suturae
Midfacial hypoplasia
Synophrys
Upward slanting eyes
Downward slanting eyes
Epicanthus (deeply covered upper and lower lip joint)*
Hypertelorism*
Strabismus
Ptosis
Low nasal bridge
High nasal bridge
Short nose*
Anteverted nostrils
Long philtrum
>3 Arches (dermatoglyphics of both hands)
Brachydactyly
Clinodactyly
Arachnodactyly
Hypoplastic fingernails (fingers or toes)
Hypoplastic phalanges*
Digital thumb
Syndactyly between fingers
Syndactyly between I and II toes
Wide gap between I and II toes
Toes overlapping
III toe as long as or longer that II toe*
Hirsutism
Haemangiomas*
Hypopigmentation
Hyperpigmentation
Pectus carinatum
Joint contractures
Abnormal elasticity of skin
Non-descended testes
Hypospadia
Hypoplastic philtrum'
Thin upper lip
Thick upper lip*
Prominent upper lip
Small mouth
Wide mouth'
Maxillar hypoplasia
Mandibular hypoplasia
Posteriorly rotated ears
Dysmorphic ears+
Low set ears
Adherent ears
Outset ears
Asymmetric ears
High arch palate
Lateral ridges
Abnormally furrowed tongue
Abnormal teeth
Low set hair
Abnormal hair
Simian crease'
Inguinal hernia
Umbilical hernia

In addition to clinical inspection the following exact measurements were taken at the 27 month assessement: (a) the largest occipitofrontal circumference (metal band), (b) philtrum length (1 mm ruler), (c) interpupillary distance (1 mm ruler), (d) distance between inner canthi (1 mm ruler), (e) distance between outer canthi (1 mm ruler), and (f) distance from upper lip to inner canthus (1 mm ruler).

The head circumference was tranformed into SD scores of Finnish normative data. Mean palpebral length was calculated by subtracting the distance between the inner canthi from the distance between the outer canthi and dividing the result by two. Palpebral length below −2SD of our non-exposed children was regarded as short.

For the analysis of relationships between the facial measurements all ratios were calculated. The following ratios will be presented in this paper: (a) distance between inner canthi/distance between outer canthi, (b) philtrum length/distance from upper lip to inner canthi, (c) philtrum length/distance between outer canthi, and (d) distance from upper lip to inner canthi/distance between out canthi.

The development level of the children was assessed by a psychologist using the manual for the Bayley scales of infant development[24] and by a speech therapist using the manual for the Reynell developmental language scales (verbal comprehension A).[16 25]

STATISTICS

The non-parametric Kruskal Wallis one way analysis of variance (3S) was used to compare the differences in the minor physical anomaly scores between the various groups; between two groups the Mann-Whitney U test was used. The difference in occurrence of two or more minor physical anomalies between the groups was tested using the χ^2 analysis and linear trend test. One way analysis of variance (ANOVA) was used to compare the morphological measurements between the groups; in pairwise analysis the Bonferroni correction was used. These measurements were also adjusted for the head circumference (ANCOVA). Differences in the occurrences of single minor physical anomalies between non-exposed and exposed children were tested for significance using Fisher's exact test for fourfold tables. A p value below 0·05 was considered significant. The computations were made using the Biomedical Data Package (BMDP).[26]

This study was accepted by the ethical committee of our hospital.

Results

The facial features of the 51 children during the first year of life are shown in table 2. All non-

Table 2 Facial features of 51 children seen during first year of life

	Normal (n=19)	*Possible FAE (n=19)*	*Typical FAS (n=10)*	*Abnormal not resembling FAS (n=3)*
Group I	9	3	1	3
Group II	8	9	1	—
Group III	2	7	8	—

exposed children were judged to have a normal looking face.

At the 27 month dysmorphic assessment we saw a significant difference between the groups in minor physical anomaly scores (table 3). Those children exposed to heavy alcohol concentrations throughout pregnancy had significantly higher minor physical anomaly scores than the children belonging to any other group (group III/any other group, $p<0·01$). There was a significant linear trend in those with two or more minor physical anomalies towards longer exposure time. Binge drinking was not connected with an increased minor physical anomaly count. No typical patterns of minor physical anomalies were formed.

Head growth was significantly affected by the duration of fetal alcohol exposure (table 4) but no differences in facial measurements were found between the groups. All horizontal distances in the eye region were significantly dependent on head circumference ($p<0·001$ for distance between outer canthi, interpupillary distance, and palpebral size; $p=0·002$ for distance between inner canthi). Vertical distances measured on the face were not dependent on the head circumference. The various relationships between the facial measurements showed no significant differences between the groups.

The single facial features mandatory for diagnosis of FAS[9] were observed more often in the exposed children; short palpebral fissure only in exposed children (table 5). No limit based on the relationships between horizontal measurements could be set to identify short palpebral fissure. The criteria of Vitez *et al* for short palpebral fissure—distance between inner canthi over one third of the distance between outer canthi—defined all the non-exposed children to have short palpebral fissure.[11] Hypoplastic philtrum and thin upper lip were observed together only in exposed children. The craniofacial criterias set by the RSA were fulfilled in two (10%) group II children and four (24%) group III children.

The six children meeting either two or three craniofacial criteria set by the RSA[9] had significantly smaller head size, interpupillary distance, distance between the outer canthi, and palpebral size (table 6). After adjustment for head circumference the mean values were smaller in the FAS group, but a significant difference was observed only in palpebral fissure length. The actual philtrum length was not significantly higher in FAS children but the ratio between philtrum length and distance from upper lip to inner canthi and the ratio between philtrum length and distance between the outer canthi were significantly higher in children who met the craniofacial criteria for FAS. However, contrary to Vitez *et al* no limit for the ratios of vertical distances could be given to define long philtrum.[11] When those features included in the craniofacial criteria for FAS were excluded from the minor physical anomaly score, these six children still had a significantly higher score (range 1–5) than non-exposed children (range 0–3) ($p<0·01$).

In order to evaluate the relationship between a subjective assessment during the first year of life and an assessment at 27 months based on strict criteria, the results of the 51 exposed children seen at both assessments were compared (table 7). All those six children who met at least two craniofacial criteria for diagnosis of FAS were judged to have a possible FAE or typical FAS face during their first year of life. However, four of the 10 children considered to have typical FAS face during their first year of life met no craniofacial criteria for FAS diagnosis at the 27 month assessment. At the 27 month assessment the 10 children assessed to have a typical FAS face during their first year of life had significantly smaller head circumference and horizontal measurements (table 6). The differences in horizontal measurements did not remain significant after adjustment for head

Table 3 Minor physical anomalies recorded per child

Group	*No of children*	*No of minor physical anomalies*							*No (%) with ≥2 minor physical anomalies†*
		0	*1*	*2*	*3*	*4*	*5*	*6*	
Non-exposed	48	26	13	5	4				9 (19)
Group I	16	7	5	3	1				4 (25)
Group II	19	4	8	3	3	1			7 (37)
Group III	16*		1	6	2	2	3	2	15 (94)

*One child excluded because of insufficient data
Kruskal-Wallis between groups: $F=31·25$, $p<0·0001$
†χ^2: $F=30·43$, $p<0·001$; linear trend: $F=24·26$, $p<0·001$

Table 4 Results of the growth and morphological measurements. Results are mean (SEM); the numbers of children excluded because of unreliable data are in parentheses

	Non-exposed (n=48)	*Group I (n=16)*	*Group II (n=19)*	*Group III (n=17)*
Head circumference (SD)	0·1 (0·15)	−0·005 (0·24)	−0·58 (0·39)	−1·494 (0·34)***
Height (SD)	−0·37 (0·12)	−0·4 (0·27)	−0·63 (0·27)	−1·45 (0·25)***
Relative weight (%)	4·26 (1·49)	1·49 (2·29)	−0·08 (2·66)	−10·46 (1·40)***
Distance between inner canthi (mm)	(2) 26·02 (0·32)	26·06 (0·78)	26 (0·5)	(1) 25·5 (0·46)
Adjusted for head circumference	25·75 (0·33)	25·94 (0·55)	25·75 (0·54)	26·09 (0·58)
Distance between outer canthi (mm)	(2) 69·48 (0·42)	69·75 (0·93)	69·3 (0·68)	(1) 67·56 (0·95)
Adjusted for head circumference	68·9 (0·71)	69·5 (0·71)	69·6 (0·7)	68·8 (0·74)
Interpupillary distance (mm)	(1) 45·87 (0·32)	45·94 (0·62)	45·23 (0·5)	(1) 44·31 (0·63)
Adjusted for head circumference	45·44 (0·32)	45·79 (0·53)	45·6 (0·52)	45·04 (0·56)
Palpebral fissure (mm)	(2) 21·73 (0·14)	21·84 (0·26)	21·68 (0·25)	(1) 21·03 (0·4)
Adjusted for head circumference	21·58 (0·16)	21·78 (0·27)	21·78 (0·26)	21·35 (0·3)
Philtrum length (mm)	14·12 (0·37)	14·87 (0·54)	14·84 (0·52)	(1) 14·62 (0·364)
Upper lip to inner canthus (mm)	(3) 42·33 (0·32)	41·99 (0·95)	41·89 (0·78)	(1) 42·2 (0·55)
Inner canthi/outer canthi	0·374 (0·003)	0·373 (0·008)	0·375 (0·005)	0·378 (0·006)
Philtrum/upper lip to inner canthus	0·336 (0·007)	0·354 (0·009)	0·354 (0·011)	0·347 (0·009)
Philtrum/outer canthi	0·204 (0·005)	0·2213 (0·008)	0·214 (0·007)	0·217 (0·007)
Upper lip to inner canthus/distance between outer canthi	0·609 (0·005)	0·602 (0·013)	0·605 (0·02)	0·626 (0·011)

***$p<0·001$ compared with non-exposed children

Table 5 Single facial features mandatory for diagnosis of FAS

	Non-exposed (n=48)	*All exposed (n=52)*	*Group I (n=16)*	*Group II (n=19)*	*Group III (n=17)*
Palpebral fissure <−2SD	0	6†	1	1	4
Hypoplastic philtrum	3	9	1	1	7
Thin upper lip	1	10*	1	2	7

*p<0·05 all exposed *v* non-exposed

Table 6 Facial measurements of exposed children meeting two or three craniofacial criteria at the 27 month assessment in the first column and of exposed children subjectively assessed to have a FAS face during their first year of life in the second column Results are mean (SEM) and are compared with those for non-exposed children (see table 4)

	27 month assessment: FAS face (n=6)	*First year assessment: FAS face (n=10)*
Head circumference (SD)	−2·58 (0·35)†††	−2·03 (0·43)†††
Distance between outer canthus (mm)	65·0 (1·05)††	65·4 (0·7)†††
Adjusted for head circumference	67·3 (1·38)	66·47 (0·96)
Interpupillary distance (mm)	43·00 (0·73)†	42·9 (0·5)†††
Adjusted for head circumference	44·6 (0·95)	43·56 (0·65)
Palpebral fissure (mm)	19·92 (0·69)†††	20·4 (0·51)†††
Adjusted for head circumference	20·45 (0·52)†	20·68 (0·38)
Philtrum length (mm)	16 (0·58)	14·9 (0·64)
Upper lip to inner canthus (mm)	41·27 (1·08)	42·9 (0·43)
Inner canthi/outer canthi	0·39 (0·009)	0·38 (0·43)
Philtrum/upper lip to inner canthus	0·39 (0·016)†	0·35 (0·012)
Philtrum/outer canthi	0·25 (0·009)††	0·23 (0·011)
Upper lip to inner canthus/distance between outer canthi	0·64 (0·027)	0·66 (0·012)†††

†p<0·05, ††p<0·01, †††p<0·001

Table 7 Comparison of a subjective assessment of facial features during the first year of life and an objective assessment at 27 months of age

At 27 months of age	*Assessment of facial features during the first year of life*			
	Normal (n=19)	*FAE (n=19)*	*FAS (n=10)*	*Atypical (n=3)*
Microcephalia	1	3	4	0
Short palpebral fissure	1	1	4	0
Hypoplastic philtrum	2	5	2	0
Thin upper lip	3	3	4	0
Two or three craniofacial criteria	0	3	3	0

circumference. The restricted growth of the head meant that these 10 children had a long midface in relation to horizontal measurements. The number of minor physical anomalies was significantly higher in children judged to have FAE features (p<0·05) and FAS features (p<0·01) compared with the non-exposed children.

Thirty two (62%) of the 52 exposed children who had undergone a thorough dysmorphic study showed poor performance in the developmental tests used at the 27 month assessment. All those six children that met the craniofacial criteria for FAS in the dysmorphic study performed under the −2SD level in the development tests. All 10 children judged to have typical FAS face during their first year of life, 12/19 judged to have possible FAS face, 1/3 judged to have abnormal face not resembling FAS, and only 8/29 judged to have normal looking face performed poorly in the used developmental tests (p<0·05).

Discussion

There is no consensus regarding the specific number and types of minor physical anomalies that should be included in a dysmorphological assessment. Studies on dysmorphology in children with alcohol exposure in utero have used varying, self constructed minor dysmorphology scales.[27 28] The 18 item weighted minor physical anomaly scale of Waldrop and Halverson[29] has been used in several studies on children with behavioural problems.[30–32] It was not accepted for this study as none of the facial features mandatory for FAS diagnosis[9] are included and several of its items are observed in over 4% of Finnish children.[21] For this study we tried to form a clinically applicable and representative minor physical anomaly scale that would include those minor physical anomalies reported in children exposed to alcohol in utero.

A significantly higher total minor physical anomaly count was observed only in those children exposed to alcohol throughout pregnancy, which is in conflict with the results of Day *et al*[27] but supports the results of Tennes and Blackard.[28] Contrary to earlier studies[10 11] we were not able to form a scoring system for various minor physical anomalies or set limits for facial relationships to identify fetal alcohol effects.

Features regarded as minor physical anomalies may be formed by several mechanisms: they can represent true malformations, disruptions, deformations, or dysplasia.[33 34] True malformations arise in the first trimester during the period of organogenesis, while other types of minor physical anomaly may be formed later during gestation. As a teratogen alcohol could interfere with an originally normal developmental process causing disruption at any stage of gestation. Frias *et al* has postulated that some observed features regarded as malformations are secondary to restricted growth of the brain.[35] Fetal hypomobility during periods of alcohol exposure in utero may also cause various deformations. Our results suggest that alcohol should be regarded as a teratogen that leads to dysmorphic features, especially during the time of rapid intrauterine growth. The inconsistent drinking patterns, one to 20 drinks per day, may explain why binge drinking was not associated with a higher minor physical anomaly count in this study.

Short palpebral fissure was a constant feature in the first children with FAS reported.[4] Jones *et al* have claimed that the short palpebral fissure in children with FAS is secondary to decreased growth of the eye.[36] This has been contradicted by Bierich *et al*[37] and Fuchs *et al*.[38] Stengel-Rutkowski *et al* have shown that normally the outer canthi lateralise more than the inner canthi with increasing age.[33] In our children the distance between the outer canthi was more dependent on head circumference than the distance between the inner canthi. Our results suggest that the short palpebral fissure seen in children exposed to alcohol in utero is mainly secondary to impaired head growth, although the possible additive influence of restricted growth of the eye could not be excluded.

The subjective assessment of facial features typical of FAS during the first year of life could not be confirmed in all cases when strict criteria were used over one year later. However, those 10 children judged to have a typical FAS face during their first year of life had significantly more minor physical anomalies than our non-exposed children, impaired head growth, and relatively long midface at the 27 month assessment as also observed by Clarren *et al.*[40] Subjective assessment of FAE or FAS features in early infancy recognised also most of those children that had been exposed prenatally to alcohol in amounts that had affected their central nervous system.

The craniofacial criteria of the RSA[9] for FAS were too strict to identify those children with clear central nervous system dysfunction but no typical FAS face.[18] It is important to learn to recognise various minor physical anomalies and subtle changes in facial relations when children with disorders of central nervous system or growth retardation of unknown aetiology are examined.

Supported by the Finnish Foundation for Alcohol Studies, Research Department of the Rinnekoti Foundation, Arvo and Lea Ylppo Foundation.

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Archives of Disease in Childhood 1992; 67: 717–719

Frontoethmoidal meningoencephalocele: a common and severe congenital abnormality in South East Asia

Christopher G M Richards

Abstract

The clinical features of 23 cases of frontoethmoidal meningoencephalocele are described in two South East Asian populations. The clinical, embryological, and epidemiological evidence may support an early teratogenic insult in the aetiology of this congenital defect.

Frontoethmoidal meningoencephalocele (FEM) is a congenital abnormality involving the herniation of meninges and cerebral tissue through a defect in the anterior cranium, between the frontal and ethmoidal bones. Although rare in Europe and the USA, the condition has been described previously in a number of racial groups in South East Asia, including Thais, Malaysians, and Burmese.

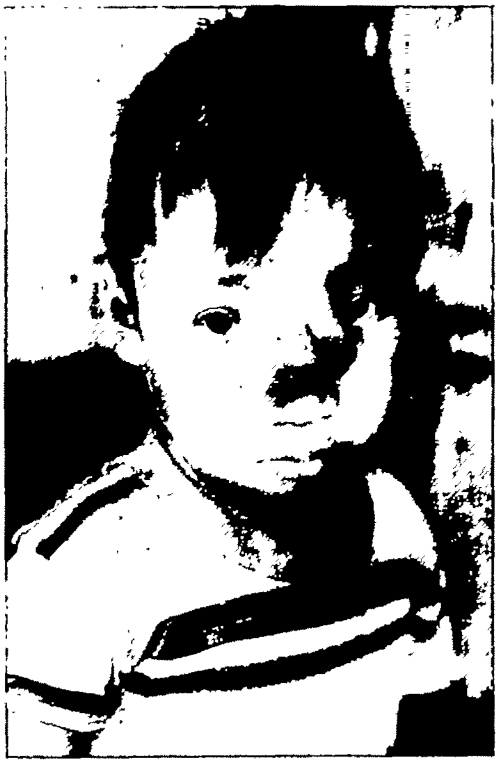
This study describes the clinical features of FEM in two ethnic groups. The Cambodian cases were detected at presentation in an outpatient facility of a refugee camp and the Thai cases were identified in an orphanage in Bangkok.

Methods and results

CAMBODIAN CASES

Seven children with FEM were seen at an outpatient facility serving a refugee camp on the Thai-Cambodian border (table and figure). Their ages ranged from newborn to 4 years with a sex distribution of five girls to two boys. All cases were diagnosed clinically.

The children presented with a progressively enlarging nasal or paranasal subcutaneous mass of which four were firm and three were fluctuant and of the latter, two were reducible. In three cases palpation of the mass caused irritation to the child, as though it was sensitive but not painful. No mass transilluminated. In two cases there was a transmitted pulsation but in neither case was there a thrill or murmur. In three cases the mass was covered by scar-like tissue which had been present since birth, and in a fourth by hyperpigmented skin containing some dark



Frontal view of 4 year old boy with a large nasal mass covered by scarring and a divergent squint.

Abnormalities associated with FEM in a Cambodian refugee camp and a Bangkok orphanage in comparison with other series

	Cambodian cases (n=7)	*Bangkok orphanage (n=16)*	*Neurosurgical referrals to Australia[1] (n=25)*	*Neurosurgical referrals in Bangkok (1966)[2] (n=25)*	*Neurosurgical referrals in Bangkok (1971*)[3] (n=100)*
Nasal mass	7	13	25	25	100
Microphthalmia	2	5	0	4	7
Anophthalmia	1	3	0	0	1
Bilateral anophthalmia	0	1	0	0	0
Corneal clouding	2	7	Not discussed	Not discussed	Not discussed
Cutaneous scar	3	13	Not discussed	Not discussed	Not discussed
Hydrocephalus	0	8	6	3	10
Microcephalus	0	3	Not discussed	5	7
Cerebral palsy	0	7	Not discussed	Not discussed	Not discussed
Female:male	5:2	4 12	12 13	11 14	Not discussed
Racial origin	Cambodian	Probably Thai	Malay (n=18), Indian (n=2), Australian aborigine (n=3), Papuan (n=1), European (n=1)	Probably Thai	Probably Thai

*1971 series probably includes cases from the 1966 series

Thai-Cambodian border

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coarse hairs. One case had a left cleft lip and palate, bilateral club feet, and an anterior anal opening in addition to the paranasal mass. Four cases had associated microphthalmia and/or anophthalmia. Two cases had partial corneal clouding. A skull radiograph revealed a frontoethmoidal bony defect in all four cases in which it was performed.

BANGKOK ORPHANAGE CASES

This institution cares for 400 handicapped children under 9 years of age. Sixteen cases of FEM were diagnosed clinically (see table). All children identified were thought to be of Thai racial origin. Their ages ranged from 2·4 to 9 years with a sex distribution of four girls to 12 boys.

All had some distortion of nasal or paranasal skin and soft tissue. In two cases there was no mass but only a distorted nasal root covered by scar-like tissue, and in a single case the only nasal abnormality was the scar-like tissue in association with anophthalmia. As in the Cambodian cases and in previous clinical studies, the site consistency, and size of the nasal mass was variable. Most were firm. Only in one case was the mass fluctuant and reducible and in no case was the mass pulsatile, transilluminable, or possessed a thrill or murmur. The associated neurological abnormalities in these cases are more severe than in the above Cambodian cases or previous series (see table). This is not surprising as case detection by presentation in outpatient departments, to neurosurgical centres, or by postal inquiry inevitably selects milder cases than would be found among children institutionalised because of mental and physical handicap. It is noteworthy, for example, that seven of the 16 cases in the orphanage were found to have spastic quadraparesis, a feature not described in other series. Similarly, 11 of the 16 cases had gross eye abnormalities in the form of microphthalmia, anophthalmia, or corneal clouding whereas in a Malaysian series none of the 25 had a gross structural eye abnormality.

Discussion

EPIDEMIOLOGY

The incidence of FEM is closely related to geographical location. A birth survey in Bangkok reported an incidence of one in 6000.[4] Prevalences of similar value were noted in a community survey in rural Thailand[4] and by postal inquiry in rural and urban Burma.[5] In contrast the condition is not described in several large birth surveys in the USA.[6] It is not known if these racial groups retain their high prevalence upon migration to temperate areas. The incidence of FEM seems to be independent of spina bifida within a defined population, providing no justification for naming the condition 'cranium bifidum' as it was originally known. If frontoethmoidal, occipital or spinal meningomyeloceles were related defects representing part of an embryonic progression then their incidences would be expected to vary directly or inversely. Neither is the case. Accordingly, the ratio of cranial to spinal meningomyeloceles treated in neurosurgical units contrasts between 1:5·2–7·4 in American studies and 3·5:1 in Thailand,[4] but spina bifida is not unduly rare in Thailand with an incidence of approximately one in 8500 live hospital births.

Two other interesting observations were made by Aung Thu and Hta Kyu in the Burmese study.[5] Conception of subjects with FEM was significantly rarer in the cold season than in rural controls, both in those attending neurosurgical centres and found by postal inquiry. They also found that the parents of cases were more often unemployed or working as rice farmers and less likely to be craftsmen or production workers than in the general population. It is not clear, however, to what extent this finding is affected by a bias of postal respondents.

In the Cambodian cases and in all but one other study, relatives of FEM cases have been unaffected. The exception was in a study by Flatz and Sukthomya who described four of 13 cases in northern Thailand who had a close relative with the condition.[7] In this study, however, information was not given about the incidence of interfamily marriages in the area or the geographical distribution of the affected cases. The lack of familial cases in most studies suggests that mendelian dominant or recessive inheritance is unlikely, although polygenic inheritance is possible.

PATHOLOGY AND EMBRYOLOGY

Postmortem studies and observations at surgical exploration show the opening in the cranium to be located between frontal and ethmoidal bones, anterior to the crista galli and cribriform plate at the site of the foramen caecum.[1,3] In one of these studies the opening was single in the midline in 40/72, bilateral on either side of the midline in 20/72, and unilateral in 12/72.[3] The herniation extrudes through the skull in various directions and locations around the site of meeting of the nasal, maxillary, and lacrimal bones. This variation together with extent of herniation explains the variety of clinical appearances. The herniation contained at least the frontal tips in 70/72 cases together with a variable quantity of brain tissue.[3] None of the 25 cases described by David *et al* showed involvement of the ventricular system in the herniation.[1] In this series, viable brain tissue was usually present at the neck of the hernia but more distal biopsy specimens showed only glial tissue.

There are a number of possible embryological explanations for the associated abnormalities in cases of FEM. Direct pressure by the hernia on orbital structures may explain the origin of anophthalmia or microphthalmia in some cases, but not in those in whom the eye abnormality occurs contralaterally to the side of prominent herniation. Although in severe cases massive herniation displaces the brain forward distorting the optic nerves,[3] which could lead to atrophy of intraorbital structures in utero, this cannot always be the alternative explanation as eye abnormalities are common in clinically mild cases. Except in cases of massive herniation forcibly expressed their commitment to raising this baby as a male in accordance with the chromosomal sex. They were averse to the alternative of gonadectomy followed by raising in the female gender with the certainty of sterility. Parents defaulted from follow up until the child was 22 months old, at which time the basal plasma testosterone concentration was less than 0·7 nmol/l with an increase to 18·4 nmol/l after hCG stimulation. The child was then not seen until the age of 6 years when phallic length was only 2 cm. A diagnosis of 5α-reductase deficiency was made based on urinary steroid analysis. Basal THF was 320 µg/24 hours, increasing to 1310 µg/24 hours after tetracosactrin stimulation. However, 5α-THF was below detectable concentrations (<50 µg/24 hours) before and after tetracosactrin stimulation. Basal urinary THF: 5α-THF ratio was greater than 6·4 (normal range for adult males: 0·61–1·43[7]) and this ratio was greater than 26·2 after tetracosactrin.

In an attempt to facilitate surgery and to improve his phenotypic appearance by increasing phallic size this boy was given a trial of DHT cream (Andractim, Laboratories Besins Iscovesco, Paris), 2·5 g applied twice daily to the phallus for three months. Phallic length and circumference before treatment were 2·5 cm and 3 cm respectively, increasing after three months to 4·5 cm and 6 cm (fig 1A and B). A stage 1 Cecil-Culp repair of the penoscrotal hypospadias was performed three months after cessation of DHT cream application, and to date there has been no reduction in phallic size despite cessation of treatment.

PATIENT 2

This child, a younger sibling of patient 1, was born in 1990 just when patient 1 was being diagnosed. The pregnancy was normal and the child weighed 3400 g at 40 weeks' gestation. Ambiguous genitalia were noted at birth with minute phallus, bifid scrotum, palpable gonads, and single urogenital sinus. Chromosomal analysis showed normal male karyotype with no mullerian structures on abdominal ultrasound. The diagnosis of 5α-reductase deficiency was made on the basis of an elevated urinary THF: 5α-THF ratio of 1·78 (normal range for young infants 0·3–0·6[7]). This ratio increased with age to 5·0 at age 2 months (fig 2) and 14·1 at 10 months. Plasma analysis after hCG stimulation showed a testosterone: DHT ratio of 12·02 at

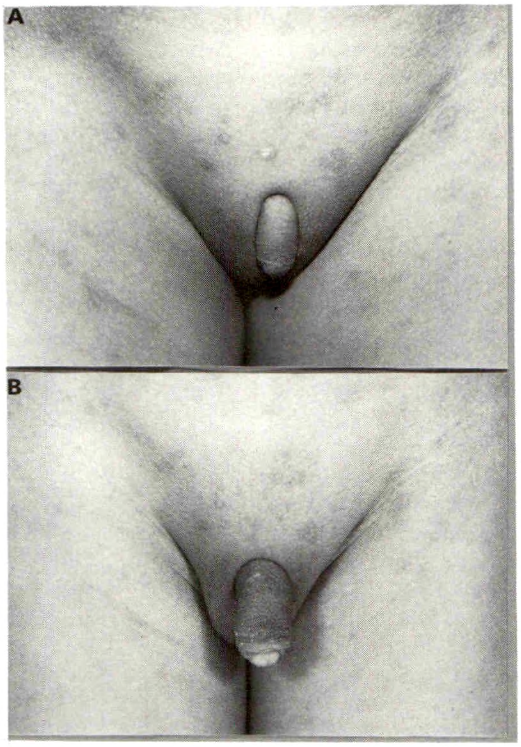

Figure 1 Patient 1 at age 6 years (A) before DHT treatment and (B) three months after DHT treatment.

Plasma steroid analysis in patient 2

	Age 3 days		*Age 9 months*		*Controls after hCG*[16]
	Basal	*After hCG*	*Basal*	*After hCG*	
Testosterone (nmol/l)	1·20	14·06	0·20	16·93	23·12 (8·60)
DHT (nmol)	0·50	1·17	0·21	0·60	1·88 (0·68)
Testosterone: DHT ratio	2·34	12·02	0·95	28·22	11·4 (1·30)

*Mean (SD) with protocol of seven injections (1500 IU/48 hours×7) in prepubertal boys (6 months–10 years).

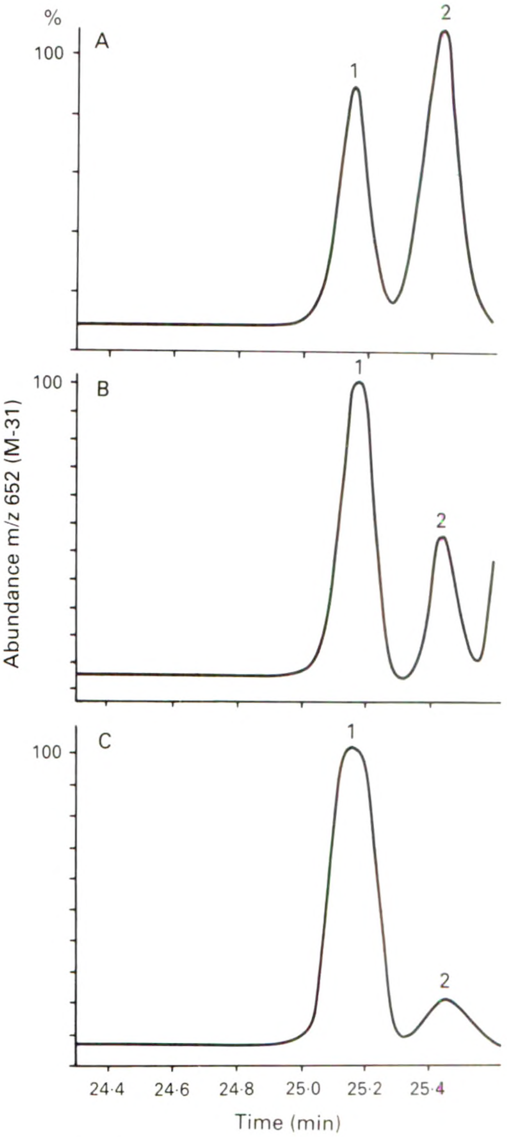

Figure 2 Urinary steroid analysis by gas capillary column chromatography/mass spectrometry. Selective analysis of ion m/z 652 (M-31) specific for THF (1) and 5α-THF (2). (A) Normal male at 3 days, THF: 5α-THF ratio=0·84; (B) patient 2 at 3 days, THF: 5α-THF ratio=1·78; (C) patient 2 aged 2 months, THF: 5α-THF ratio=5·0.

age 3 days and this ratio increased to 28·22 at age 9 months (table).

The child received a six months' course of DHT cream applied to the phallus twice daily, and an increase in phallic length from 0·5 cm to 2·6 cm was observed.

Discussion

The birth of a baby with ambiguous genitalia is extremely distressing for the parents, and the clinician needs to establish the correct diagnosis and the appropriate decision regarding gender assignment as quickly as possible, taking into account the cultural and religious beliefs of the parents. In this family, the parents were practising Muslims and the rearing of the first son as a castrated female was unacceptable. Fortunately this proved to be the correct decision but it was not until the child was 6 years old that the correct diagnosis was made. Even with the knowledge that the elder brother had 5α-reductase deficiency the initial decision regarding the gender in the younger sibling was difficult. The external genitalia were extremely poorly virilised even when compared with the older brother at a similar age. An early clinical decision to advise the parents to raise as a male was taken after the diagnosis of 5α-reductase deficiency based on the urine steroid metabolite abnormality detected at day 3. By contrast, plasma DHT and testosterone:DHT ratio at 3 days were within normal range, becoming abnormal with age (table). It has been previously suggested that the hCG stimulation is a reliable diagnostic test for the condition in infancy,[1 5 8] however the normal result at 3 days in patient 2 could have led to misdiagnosis and illustrates the need to measure both plasma and urinary steroids, and to repeat these tests a few weeks later when studying neonates suspected of suffering from this disorder. It is apparent from our experience that urinary steroid analysis is a more sensitive diagnostic test than hCG stimulation in neonates.

Spontaneous virilisation at puberty is well described in 5α-reductase deficiency, especially in affected persons from the Dominican Republic in whom successful evolution of male gender identity occurs.[17 18] However, with the exception of the Dominican Republic where the condition is socially acceptable, an affected person is vulnerable to the psychological effects of ambiguous genitalia during the childhood period. It is for this reason that corrective surgery was required in patient 1. The application of DHT cream promoted phallic growth in patient 1 sufficient to cause an improvement in male appearance as well as greatly facilitating surgery. In patient 2 DHT cream caused sufficient phallic growth to relieve parental anxiety and provided some assurance that the diagnosis and prognosis were correct.

We suggest that in the context of male pseudohermaphroditism with normal or raised concentrations of testosterone, phallic growth in response to DHT cream application could be an indirect confirmation of 5α-reductase deficiency. DHT cream treatment is certainly of benefit in improving the phenotypic appearance in affected individuals as well as facilitating reconstructive surgery.

We thank Dr Maguelone G Forest, Hopital Debrousse, Lyon, France for plasma testosterone and dihydrotestosterone evaluations in patient 2. The THF: 5α-THF ratios in patient 2 were performed by Dr Cedric Shackleton, Childrens Hospital, Oakland, California who is supported by the National Institute of Health (grant DK 34400).

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Addendum

Since submission of this paper additional relevant information has been published.[1] This research confirms the presence of two functional 5α-reductase genes in man but only one of the genes was abnormal in two related individuals with pseudohermaphroditism due to 5α-reductase deficiency. An explanation for the difficulties we encountered in diagnosing 5α-reductase deficiency in early infancy is now possible. If there is high activity of the unaffeced where occlusion of the foramen of Monroe has been described, it remains to be explained why so many cases develop hydrocephalus. The presence of nasal scar-like tissue is also a striking feature of this condition that has yet to be explained. This might be caused by in utero exposure of unepithelialised herniation with later epithelialisation to form this curious area of defective skin.

The simplest explanation is that the various abnormalities originate from a defect in cell development or migration at the stage of the three week embryo when eye and neural fields lie in close proximity. FEM have been found associated with holotelencephaly,[2] supporting the idea that the defective step is early in development. The three week embryo predates formation of cartilage or ossification centres and therefore it may be that, unlike most other types of hernia, the contents, not the defect in the wall, is the primary abnormality. The presence of anterior and posterior fontanelles throughout fetal life provides evidence that the normally developing brain does not breech a meningeal covered break in the cranial vault.

AETIOLOGY—A HYPOTHESIS

Some of the epidemiological and pathological evidence supports the idea that a FEM is a consequence of a teratogenic insult. Favoured candidates proposed by Aung Thu and Hta Kya are the aflatoxins, produced by one genus of the imperfect fungi, aspergillus.[5] These toxins have been found in food samples taken from markets in Thailand and in the secretions and tissues of well and sick Thai children.[8] One of the aflatoxins, ochratoxin A, has been shown to induce a range of gross abnormalities—including exencephaly, anophthalmia and cleft lip—in mouse fetuses after a single intraperitoneal injection of the pregnant adult on day 7–12.[9] Such toxins may be present in the diet in higher concentrations during the hot, humid months and when foodstuffs are stored for long periods in poorly ventilated rooms. This hypothesis is consistent with the bias away from cold season conception among cases of FEM and the higher incidence among the children of poor rice farmers and the unemployed reported in the Burmese study.[5]

The hypothesis could be tested in a number of ways. The incidence of the condition at birth could be recorded in a defined population before and after elimination of the aflatoxins from the diet. However, one alarming feature of these toxins is that they are not eliminated by cooking.[10] Treatment of food with ammonia, sodium hypochlorite, or hydrogen peroxide may provide a more effective means of removing the toxin.[11] Another approach would be to use a mammalian model to study the effects of the specific type of aflatoxin that might be found in the blood of pregnant women living in areas where FEM is common, although the possible species specific nature of the toxin's teratogenic effect may make these observations hard to interpret.

I am grateful to Janet Taylor in helping to collect clinical informatin on the Cambodian cases

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Archives of Disease in Childhood 1992; 67: 720–723

Early diagnosis and management of 5α-reductase deficiency

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Abstract

Two siblings of Pakistani origin, karyotype 46 XY, were born with predominantly female external genitalia with minute phallus, bifid scrotum, urogenital sinus, and palpable gonads. The older sibling at the age of 8 days showed an adequate testosterone response to human chorionic gonadotrophin (hCG) stimulation. The diagnosis of 5α-reductase deficiency was made at age 6 years when no 5α-reduced glucocorticoid metabolites were detectable in urine even after tetracosactrin (Synacthen) stimulation. In the younger sibling the diagnosis of 5α-reductase deficiency was provisionally made at the early age of 3 days on the basis of high urinary tetrahydrocortisol (THF)/allotetrahydrocortisol (5 α-THF) ratio and this ratio increased with age confirming the diagnosis. Plasma testosterone: dihydrotestosterone (DHT) ratio before and after hCG stimulation was within normal limits at age 3 days but was raised at age 9 months. Topical DHT cream application to the external genitalia promoted significant phallic growth in both siblings and in the older sibling corrective surgery was facilitated. In prepubertal male pseudohermaphrodites with normal or raised testosterone concentrations, phallic growth in response to DHT cream treatment could be an indirect confirmation of 5α-reductase deficiency.

Deficiency of 5α-reductase was described as a distinct biochemical entity in 1974.[1,2] The condition is inherited as an autosomal recessive disorder and is characterised by external female phenotype at birth, presence of bilateral testes and normally developed internal male genitalia, including seminal vesicles and ejaculatory duct, while at puberty there is variable virilisation of the external genitalia accompanied by the development of pubic and axillary hair.[1–4]

The biochemical abnormalities characteristic of 5α-reductase deficiency are clearly described in adults and older children but it is only recently that the diagnosis has been made in infancy, the critical period for sex determination in the newborn with ambiguous genitalia.[3,5–7] The typical pattern is that of normal or raised concentration of plasma testosterone with decreased dihydrotestosterone (DHT) and increased testosterone: DHT ratio especially after human chorionic gonadotrophin (hCG) stimulation[5,6,8] Additional abnormalities include reduced levels of 5α-reduced urinary glucocorticoid and androgen metabolites, for example, allotetrahydrocortisol (5α-THF) and androsterone.[9,10] In infancy measurement of these steroid metabolites can be difficult as they are present at low concentrations in the presence of high concentrations of steroid metabolites of similar structure. Sensitive detection methods of high specificity (for example, gas chromatography/mass spectrometry) are therefore required.[7] Decreased 5α-reductase activity in fibroblasts cultured from genital skin may also aid diagnosis.[11,12]

We describe two siblings with 5α-reductase deficiency, the younger of whom was diagnosed shortly after birth. In both siblings DHT treatment was of value in increasing phallic size.

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Methods

hCG stimulation was performed by giving 1000 IU of hCG daily for three days. Plasma samples for testosterone and DHT measurements were taken on days 0 and 4.[13] The tetracosactrin (Synacthen, Ciba) stimulation test was performed by administering tetracosactrin 250 μg as a six hour infusion. Twenty four hour urine samples were collected before and after the infusion for the measurement of THF and 5α-THF. Plasma testosterone and DHT were measured with a specific radioimmunoassay after ether extraction and celite column chromatography.[14]

Urinary steroid metabolites were measured by a method based on that of Shackleton and Honour using capillary column chromatography linked either to a flame ionisation detector (patient 1) or to a mass spectrometer (patient 2). Selective measurement of THF and 5α-THF was performed by monitoring ion m/z 652 (M-31) of the methyloxime-trimethysilyl ether derivative.[15]

Case reports

PATIENT 1

This child, born in 1983, was the second child of Pakistani parents who were first cousins and practising Muslims. The pregnancy was normal and the child weighed 3100 g at 40 weeks' gestation. Examination at birth revealed micropenis with bifid scrotum, penoscrotal hypospadias, and palpable gonads in the labioscrotal folds. Karyotype was normal male, and no mullerian structures were seen on abdominal ultrasound.

At age 8 days basal plasma testosterone concentration was 6·3 nmol/l and an increase to 16·0 nmol/l was demonstrated after hCG stimulation. A diagnosis of incomplete androgen insensitivity was made, having excluded a biosynthetic defect of testosterone, but the parents

5α-reductase during the neonatal period this could result in normal production of DHT. The activity of this enzyme may decrease rapidly with age but residual activity could account for the fact that even in older patients with 5α-reductase deficiency low but detectable concentrations of dihydrotestosterone are present. At all times the affected enzyme causes a decrease in hepatic 5α-reductase leading to low excretion of 5α-THF allowing biochemical detection of the abnormality. More studies on the 5α-reductase activities during the first few weeks of life are now required to further establish this hypothesis.

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When is a haemangioma not a haemangioma?

Many congenital dysmorphic syndromes are said to have vascular anomalies of the skin as a feature and these anomalies are often referred to as haemangiomas. A recent article from Harvard Medical School (A Jay Burns and colleagues, *Pediatrics* 1991;**88**: 1257–67) points out that these lesions are rarely true haemangiomas. The authors classify vascular birthmarks into three types: haemangiomas, vascular malformations, and macular stains. Haemangiomas as they define them seem identical with what most of us know as strawberry marks. Their main characteristic is their rapid early growth and their bulk and they differ histologically from other types of vascular anomaly. Vascular malformations grow only in pace with the child and are permanent. They may be capillary (port wine stain), venous, arteriovenous, lymphatic, or mixed. Macular stains are those lesions which are commonly found over the glabellar region, the upper eyelids, and the nape of the neck and are referred to as stork beak marks or nevus flammeus. These authors reviewed the main textbook descriptions and papers concerning congenital dysmorphic syndromes and associated vascular anomalies. Such anomalies are often described in dsymorphic syndromes and are frequently described as angiomas or haemangiomas but most of them are really either macular stains or vascular malformations. Macular stains are seen in 30 to 40% of normal children and the significance of their association with rare dysmorphic syndromes is open to question. The list of syndromes in which they are said to occur includes fetal alcohol syndrome, Rubinstein-Taybi, Beckwith-Wiedemann, Edwards, Patau, and several others.

Capillary malformations are, of course, seen in the Sturge-Weber syndrome and lymphatic malformations in Turner's and Noonan's syndromes. A list of 20 syndromes is given in which complex vascular malformations, venous malformations, and telangiectases (a variety of capillary malformations) are described.

Very few syndromes have true haemangiomas as a feature. They give a list of three: coarctation of a right sided aortic arch, cleft sternum or upper mid-line abdominal wall defect, and sacral defects, tethered spinal cord, and various genitourinary defects.

It seems that the writers of textbooks will need to be more precise in their classification of vascular birthmarks in future.

ARCHIVIST

Archives of Disease in Childhood 1992; **67**: 724–727

Salivary IgA antigliadin antibody as a marker for coeliac disease

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Abstract

In recent years, serum antibodies to gliadin (AGA) have been reported to be useful markers of coeliac disease. IgA AGA have also been found in intestinal secretions and saliva in coeliac disease and may offer a convenient, non-invasive screening test. In order to test this hypothesis, salivary and serum AGA were measured in children with coeliac disease proved by biopsy and compared with several control groups. Measurement of salivary IgA AGA provided excellent discrimination between those children with coeliac disease and the control groups, and our study suggests that it may provide a rapid, non-invasive method of screening for this disease before intestinal biopsy.

Coeliac disease remains an important cause of malabsorption in children. Definitive diagnosis requires histological confirmation by jejunal biopsy showing subtotal villous atrophy, increased numbers of intraepithelial lymphocytes, and crypt cell hyperplasia. Small intestinal biopsy is invasive, involves a period of fasting, and requires exposure to radiation to confirm correct positioning of the capsule. Many children undergo biopsies that subsequently prove to be negative, and thus various non-invasive tests have been proposed as screening tests. Tests such as xylose absorption and differential sugar permeability lack specificity and may be falsely positive in children with other causes of small intestinal mucosal damage.[1] Recently, attention has been directed towards the measurement of serum antibodies to gliadin,[2–9] smooth muscle endomysium,[8–12] reticulin,[12–14] and human jejunum,[15] with different workers finding varying degrees of specificity and sensitivity for these tests. Antigliadin antibodies (AGA) are also known to be present in the intestinal secretions and saliva of patients with coeliac disease[16–20] and measurement of these might therefore provide a useful screening test.

A preliminary study reported in Cardiff suggested that measurement of salivary IgA AGA might be a reliable marker for coeliac disease in adults.[21] Such a screening test would have obvious potential benefits in childhood and might reduce the need for more invasive tests involving blood sampling. The aim of this present study was to determine the usefulness of the test in childhood and to compare the results with serum measurements of IgA and IgG AGA.

Patients and methods

A prospective study was designed to determine the prevalence of salivary and serum IgA AGA and serum IgG AGA in groups of children with coeliac disease, other gastrointestinal disorders, cystic fibrosis, and in children with no evidence of gut disease.

PATIENTS

There were 141 patients, divided into five groups, in whom AGA were measured. In group A were 19 patients (age range 9 months–14 years, median 5 years) who had coeliac disease proved by biopsy: they comprised 16 studied at presentation and three after gluten challenge. In group B were nine children (age range 2–18 years, median 6 years) who had established coeliac disease and were clinically well on a gluten free diet. Both these groups had satisfied the revised European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) criteria for diagnosis.[22] In group C were 60 children (age range 6 months–15 years, median 4 years) undergoing jejunal biopsy who subsequently proved to have conditions other than coeliac disease (such as cows' milk or soy protein intolerance or toddler diarrhoea). In group D were nine children (age range 1–13 years, median 9 years) with cystic fibrosis. In group E were 44 children (age range 6 months to 18 years, median 4 years) with no clinical evidence of gastrointestinal disease who were having blood tests for other reasons. Small intestinal histology was not available for the last two groups of children.

It proved impossible to collect both serum and saliva in every patient in each group and the results represent all the data available in each group of patients. Simultaneous saliva and serum data were, however, available in eight patients. The district ethical committee had approved the study and consent was obtained from all parents and from older children if possible.

METHODS

Whole unstimulated saliva was collected from the patients. Older children were able to spit directly into sterile containers and, for younger children and infants, a suction catheter attached to gentle wall suction was used to obtain the specimens. At least 1 ml was obtained from each child. The saliva was heated at 56°C for 30 minutes to inactivate complement and enzyme activity, and centrifuged at 1000 *g* for 20 minutes to remove particulate matter. The supernatant was stored at −20°C until the assays were performed. Salivary IgA AGA were assayed using a standard enzyme linked immunosorbent assay (ELISA) technique as previously described.[21]

For the serum assays, a commercial gliadin IgA ELISA test kit (Pharmacia) was used and a similar ELISA technique (in another laboratory) was used to measure serum IgG AGA. The results for each assay were expressed in optical density units and the results of saliva and serum antibodies from each group were compared and analysed by non-parametric means using the Mann–Whitney U test.

Results

Table 1 shows the numbers of patients studied and the median IgA AGA values for each group with fig 1–3 showing the individual results.

Salivary IgA AGA (fig 1)

It is clear that AGA concentrations were significantly higher in patients with untreated coeliac disease compared with the patients in the other groups ($p<0·0001$ in each case). All patients with untreated coeliac disease had salivary IgA AGA concentrations >0·31 optical density units. Using this value as an arbitrary limit to achieve 100% sensitivity for the test, there were seven values >0·31 in the other groups (false positive vaues), giving the test a specificity of 90%. In these seven children, the jejunal histology showed partial villous atrophy in four (clinical diagnosis of cows' milk protein intolerance in each case) and was normal in three (clinical diagnosis of toddler diarrhoea in each case).

Serum IgA AGA (fig 2)

As data for both salivary and serum IgA AGA were not available from all patients, the patient

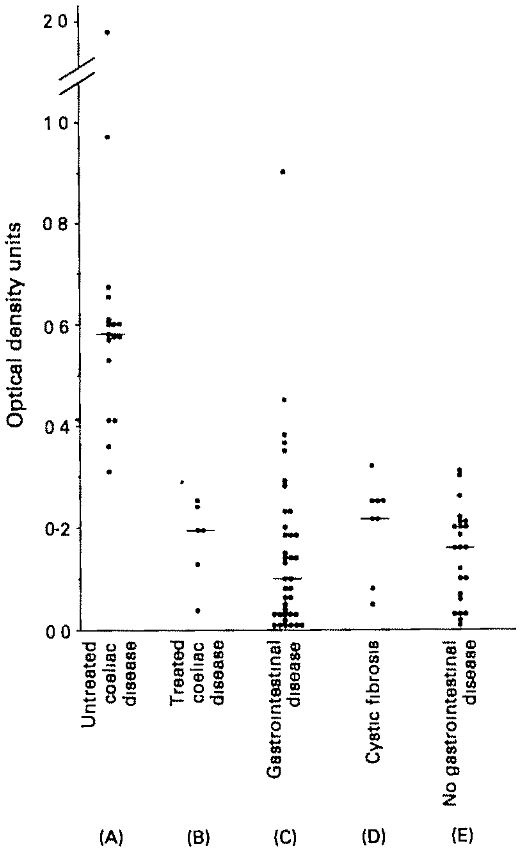

Figure 1 IgA antibodies to crude gliadin in whole unstimulated saliva.

Table 1 Salivary IgA AGA

	No studied	*Optical density units*	
		Range	*Median*
(A) Untreated coeliac disease	17	0·309–1·894	0·594
(B) Coeliac disease on gluten free diet	6	0·039–0·252	0·195
(C) Other gastrointestinal disease	38	0·010–0·450	0·100
(D) Cystic fibrosis	7	0·051–0·248	0·219
(E) No gastrointestinal disease disorder	23	0·012–0·300	0·155

Table 2 Serum IgA AGA

	No studied	*Optical density units*	
		Range	*Median*
(A) Untreated coeliac disease	15	2–136	45
(B) Coeliac disease on gluten free diet	7	4–11	6
(C) Other gastrointestinal disease	53	1–16	5
(D) Cystic fibrosis	9	1–17	7
(E) No gastrointestinal disease disorder	29	1–49	7

Table 3 Serum IgG AGA

	No studied	*Optical density units*	
		Range	*Median*
(A) Untreated coeliac disease	7	1·84–18·40	9·7
(B) Coeliac disease on gluten free diet	3	0·7–5·42	2·36
(C) Other gastrointestinal disease	37	0·32–11·30	1·56
(D) Cystic fibrosis	7	0·3–26·40	0·95
(E) No gastrointestinal disease disorder	16	1·09–14·00	1·4

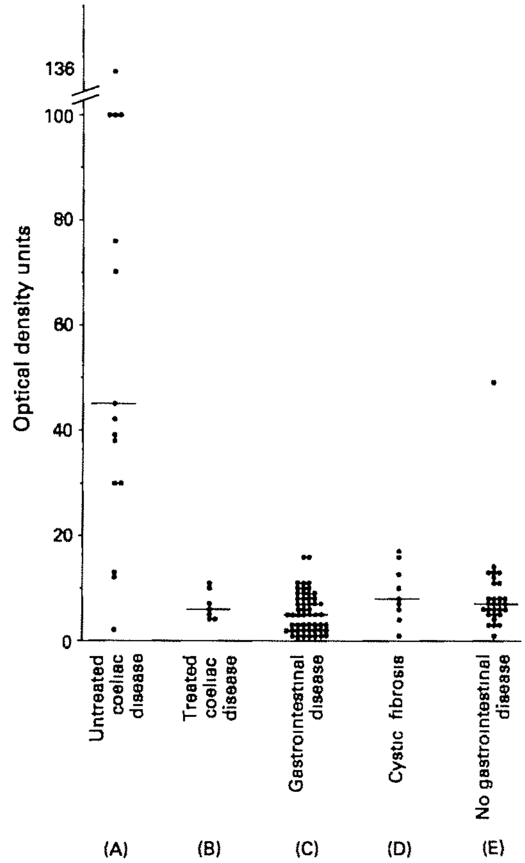

Figure 2 IgA antibodies to gliadin in serum.

numbers are different from those shown in table 1. The results in untreated coeliac disease were significantly higher than in all other groups (fig 2). The 'normal' reference range quoted for the test by Pharmacia is 0–25 and, using this range, three of the 15 patients with untreated coeliac disease had normal values (false negative results), giving the test a sensitivity of 80%. All the patients in the other groups, with one exception, gave results within the quoted normal range, yielding a specificity of 99%.

In the eight patients with coeliac disease in whom saliva and serum AGA were studied simultaneously, there was no correlation between the individual results for salivary and serum IgA. Thus some patients registered high levels of AGA in saliva and low levels in serum, and vice versa.

Serum IgG AGA (fig 3)

Unfortunately, data were available from a relatively small number of patients and, although the median value in the group with untreated coeliac disease was much higher than in the other groups, there was considerable overlap with very high values occurring in children who did not have coeliac disease.

There were no age related differences in values of AGA in saliva or serum in any of the groups (data not shown).

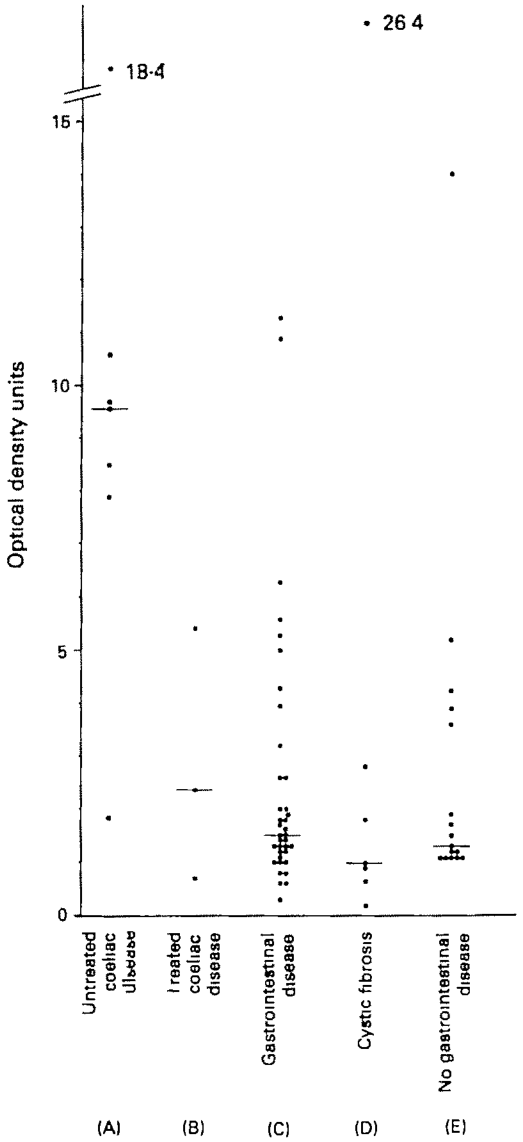

Figure 3 IgG antibodies to gliadin in serum

Discussion

The definitive diagnosis of coeliac disease still requires small intestinal biopsy, which is invasive and time consuming, and many negative biopsies are performed each year. Early diagnosis of the condition is important, not only in avoiding the clinical consequences of malabsorption and suboptimal growth, but also because treatment with a gluten free diet appears to reduce the subsequent risk of small intestinal malignancy.[23]

In order to minimise the number of negative biopsies, several non-invasive screening tests have been employed and, of these, the use of serological markers has proved to be the most fruitful.[24] Thus measurement of serum antibodies to gliadin, reticulin, smooth muscle endomysium, and human jejunum have been employed and various researchers have reported acceptable levels of sensitivity and specificity.[2–15]

Little is know about mucosal immunity in this condition and the relationship between the antibody concentrations in blood and those in intestinal secretions. Gliadin in the gut lumen is thought to stimulate IgA precursor lymphocytes in the gut associated lymphoid tissue. The precursor lymphocytes differentiate into IgA-producing plasma cells and secrete IgA AGA that enter the intestinal secretions. These precursor lymphocytes also populate mucosal tissues and remote secretory glands such as the salivary glands, resulting in the appearance of IgA AGA in saliva.[25] The salivary glands are considered part of the common mucosal immune system although it has been recently suggested that, in adults, salivary antibodies may not reflect intestinal humoral immunity.[20] Other data suggest that the measurement of salivary antigliadin antibodies may be a reliable marker for coeliac disease in adult patients[21] and the aim of our study was to assess their usefulness in childhood.

Our results suggest that measurement of IgA AGA in saliva may be very useful as a screening test for coeliac disease with acceptable levels of sensitivity and specificity. Indeed, using an arbitrary cut off level for our assay in order to obtain 100% sensitivity for coeliac disease, the test remained highly specific. The measurement of serum IgA antibodies using a widely available commercial test kit was less sensitive and, using the kit's quoted reference range, would have missed an unacceptable number of biopsy proved cases of coeliac disease. In the context of screening children for coeliac disease, a salivary IgA AGA test with 100% sensitivity but with 10% false positives is preferable to serum IgA AGA assay with 20% false negative findings. Interestingly, there was poor correlation between salivary and serum IgA AGA in individual patients with untreated coeliac disease and, in our hands, as other workers have suggested, measurement of IgG AGA is too non-specific to be of clinical usefulness if considered in isolation.[1]

The incidence of IgA deficiency is said to be increased in coeliac disease[4 26] and measurement of IgA antibodies alone may theoretically miss these cases. For this reason measurement of both IgA and IgG antibodies may be more helpful.

Measurement of salivary antibodies is simple, rapid and non-invasive, which would be of great benefit in the investigation of children. Although further studies are needed to confirm the usefulness of salivary antibody measurement and its superiority over serum antibody measurement, a test involving saliva may well prove to be a more acceptable screening tool for coeliac disease before jejunal biopsy than one involving venepuncture.

We would like to thank Dr Robert Newcombe for his assistance with statistical analysis and Miss Leah Gallivan for typing the manuscript.

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Archives of Disease in Childhood 1992; 67: 728–730

Late diagnosis of cryptorchidism: a failure of medical screening?

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Abstract

A retropective review of hospital and available community records of 47 children undergoing orchidopexy in a district hospital was undertaken to determine adequacy of screening for cryptorchidism and factors associated with late referral. Twenty eight of these boys were previously examined on 108 occasions. Diagnosis was missed on 32 occasions and the record of 28 clinical examinations did not include position of testes. In the case of 16 boys (four under school age and 12 of school age) appropriate action was not taken once the diagnosis was made. Diagnosis was reliably made in school aged children but in children under the age of 1 year cryptorchidism was frequently missed by the examining doctor. It is suggested that criteria for diagnosis and referral should be agreed in any surveillance programme. Junior doctors in hospital responsible for routine clinical examination of children during admission and clinical medical officers or general practitioners during routine clinical examination of boys should be clearly instructed to examine and record the position of the testes.

The testis arises from the germinal ridge on the posterior abdominal wall medial to the developing kidney, joins with the epididymis and vas deferens, and then descends into the scrotum. The testis lies at the iliac fossa at 3 months and within the inguinal canal at 7 months of intrauterine life. By 8 months it is entering the scrotum and by birth in the full term infant it should be in the scrotum.[1]

If for any reason the descent of the testis is arrested in its normal pathway, the condition is described as undescended testis. If the testis deviates from its normal course of descent the condition is called ectopic testis. In both conditions the testis is absent from the scrotal sac and this is usually described as cryptorchidism, which can be bilateral or unilateral.

The incidence of cryptorchidism is reported to be rising,[2 3] and has recently been found to be 1·6% in boys at the age of 3 months. The incidence is higher at birth and higher still in preterm babies.[2] It becomes significantly less by the age of 3 months, because in some babies the testis descends during the first three months of life.

After the age of 3 months the testis does not descend any further. In some cases a descended testis is found to be undescended again at a later age.[4] This is usually where the testis is absent from the scrotal sac at birth and descends during the first three months of life.[5]

If a testis is left in its undescended or maldescended position for a prolonged period there are risks of atrophy, torsion, malignant changes, and subfertility. Atrophic changes have been described at 2 years.[6] Therefore, it seems essential that cases of cryptorchidism are diagnosed early and treated early.

It has been suggested that the age of diagnosis of cryptorchidism in a district is an important measure of the effectiveness of the child health surveillance programme, and it should be one of the criteria to be used for auditing the service.[7 8]

Subjects and methods

All boys admitted for orchidopexy into the paediatric ward of a district general hospital during the year 1989 were included in this study. These children were admitted to the ward for orchidopexy after being seen by a member of the surgical team as an inpatient or as an outpatient.

The district hospital was located in a London suburban district with a population of 230 000 of whom 40 000 were under 15 years of age. The annual birth rate at the maternity hospital of the district was 3000. The district child health surveillance programme made provision for all children to be examined by a clinical medical officer at the age of 6 weeks, 15–18 months, and at school entry.

All new entrants to local schools were offered a clinical examination by a doctor when there was no record of a medical examination at or around school age. Although the exact uptake of these examinations were not available, it could be assumed that 90% of the boys would have had at least one medical examination by a doctor within two years of school entry. Some 1700 clinical medical officer sessions were used for routine child health surveillance in the district in 1989.

In addition all newborn babies were routinely examined by a doctor within the first 24 hours of birth and again before discharge. Annually the paediatric department and casualty department of the hospital between them saw 15 000 childhood cases (approximate average over the last few years).

Results

There were 47 admissions for orchidopexy. Hospital notes of all 47 boys were reviewed together with community child health notes of 33 boys; 14 children lived outside the borough, and their community records were not obtainable. Of the 47 boys, 13 had bilateral cryptorchidism and 16 had left sided cryptorchidism.

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Accepted 4 February 1992

The longest waiting time after referral was two years (except for the seven children diagnosed below the age of 3 years). However, only 17% of these were operated upon under the age of 5 years.

The following examples are specially listed to highlight some of the missed opportunities for early treatment and diagnosis.

(1) In the case of four boys the condition was diagnosed before the age of 4 years, but no action was taken.

(2) In 12 other boys diagnosis was made after the age of 5 years but they were called up for review before being referred to surgeons; two such boys missed review appointments and referral was delayed by more than one year.

(3) Of two boys who had orchidectomy, one was diagnosed at the age of 4 years but his parents refused referral to hospital until the age of 6 years, when he had a first stage orchidopexy but did not turn up for the second stage operation for a long time; at the time of operation the testis was atrophic and was excised. The other boy missed his initial call for operation and suffered from a torsion of the undescended testis before admission to hospital.

(4) Two boys with bilateral undescended testes underwent orchidopexy on one side but were not followed up and needed to be referred again to the surgeons.

(5) Two patients were admitted to a special care nursery in the neonatal period but the diagnosis was missed. The other patient, who had right sided orchidopexy at the age of 10 years, was surgically treated for congenital pyloric stenosis at the age of 6 weeks and was followed up for a suspected right sided inguinal hernia but was lost from follow up subsequently.

(6) One patient was diagnosed as having right sided undescended testis in the newborn period but the testis descended by 6 months of age and he was discharged from follow up. He underwent right sided orchidopexy at the age of 10 years.

(7) One boy was seen repeatedly in a regional centre for developmental delay but undescended testis was missed. One patient was admitted to a children's hospital for bronchial asthma but undescended testis was not diagnosed.

Table 1 Age at orchidopexy/orchidectomy (n=47)

Age (years)	3	4	5	6	7	8	9	10	11	12
No of boys	1	7	7	3	7	7	3	7	1	4

Table 2 Recording in the notes of the position of testes after a clinical examination of doctors working in community child health, the paediatric department, and in other departments within the hospital

Age at examination	*Group of doctors**	*No of examinations*	*Position of testes*		
			Unrecorded	*Correctly recorded*	*Incorrectly recorded*
0–3 months	Community	18	6	3	9
	Paediatrics	4	2	1	1
	Others	1	0	0	1
3 months-4 years	Community	20	13	1	6
	Paediatrics	14	6	2	6
	Others	3	2	1	0
4 years and over	Community	33	4	24	5
	Paediatrics	6	1	5	0
	Others	9	4	1	4
Total		108	38	38	32

*Comunity=clinical medical officers/senior clinical medical offiers, paediatrics=senior and junior doctors of the paediatric departments, and others=senior and junior doctors working in other specialities within the hospital

The 47 boys referred to the surgery department included two under 1 year of age, referred from the maternity hospital, five aged 1–3 of whom three were referred by surgeons, one from a child health clinic, and one from the child development centre. The 40 children aged 4 or more included 19 referred from the child health clinics, 15 referred by general practitioners, and one each from the paediatric department, surgeons from another district, and from the accident and emergency department. In the remaining three the source of referral was unclear.

The number of boys referred by general practitioners included two boys diagnosed by their mother and a number who were diagnosed by clinical medical officers, but referred through their general practitioners. Of three boys referred by the surgeons themselves, diagnosis was made when two were admitted for circumcision and one for abdominal pain.

Table 1 summarises the age distribution of these boys. Age in this table was calculated in years at their last birthday before orchidopexy. Table 2 shows the number of times these children were examined before admission to hospital for orchidopexy. In this table only a general clinical examination done for the purpose of making a medical assessment was included. Examinations without an entry in the case notes indicating that an abdominal examination or a systematic examination was carried out were excluded.

Examinations of the same boy at different consultations were listed as separate examinations. The clinical examinations carried out by the community medical officer were done either as part of a routine surveillance check or as part of a consultation done for other symptoms. The clinical examinations carried out by hospital doctors included examinations done in outpatient clinics and in the ward. Most of these examinations were carried out by senior house officers, but a small number were undertaken by registrars or consultants.

Discussion

There were other district general hospitals and children's hospitals where children from the district might undergo orchidopexy. Similarly, children from neighbouring districts are admitted for orchidopexy and were included in this study.

The figures for orchidopexy in the hospital would not reflect the incidence of cryptorchidism in the district population. The neonatal notes could not be reviewed for three main reasons: (i) many boys were born outside the district, (ii) the common practice of recording findings of routine neonatal examination in maternal records, and (iii) frequent changes in name and address.

Although there is considerable doubt about the benefit of early surgery for cryptorchidism in preventing future malignancy and subfertility, social, psychological, and clincal factors favour early surgery The recent trend has been to operate early.[9,10] However, although most surgeons in a group of district hospitals favoured surgery below school age, only 32% of orchidopexies were done under 5 years.[11] The average age at orchidopexy has been reported as 6 years[1] and 7 years.[10] The average age of surgery in this group of boys was rather higher with more than 50% of the boys 7 years or older. Only 17% of the children were of preschool age.

These results illustrated some causes for delay in surgery.

(1) Undescended testis was frequently missed by doctors during the first year of life; this has been previously reported.[12] The reasons for this were not clear. It could be that some incompletely descended testes lying in the upper part of the scrotum were wrongly diagnosed as completely descended. Simple clinical criteria have been shown to be as reliable as complicated measurements in detection of cryptorchidism.[2] Failure of detection at an early age resulted in most boys being more than 5 years at the time of diagnosis.

(2) There was unnecessary delay in referral to surgeons once the diagnosis was made even when the child was over 5 years of age. This resulted from lack of clear guidelines to the screening doctors. This delay was recently highlighted in another paper.[10]

(3) Some boys could have been diagnosed by the hospital doctors if testes of all boys were routinely examined during medical assessment. Nineteen of the 47 boys were diagnosed at school medical examination suggesting a continuing value for routine medical examination at school entry. A selective screening procedure, as suggested recently,[13] would probably result in further delay in diagnosis.

CONCLUSION

In general the diagnosis and management of cryptorchidism in this district has been far from satisfactory. Similar findings have been reported from other centres. To improve the diagnosis and management of cryptorchidism the following recommendations are made:

(1) Doctors and other health workers undertaking surveillance procedures should be adequately trained in the technique of examining testes of young babies and children.

(2) Routine surveillance examinations should include examination of male genitalia and recording the findings in the case record.

(3) Junior doctors in all departments dealing with children should be instructed to include examination of male genitalia in all routine medical examinations.

(4) Every district should have clear policies directing doctors to refer boys over 6 months with undescended testis to surgeons.

(5) Babies who are born with undescended testis should be seen at approximately 12 months, even if the testis appeared descended by the age of 6 months or so.

(6) Physical examination at or about the age of school entry remains an effective screening examination for cryptorchidism.

I am most grateful to Dr AMB Golding and Professor BW Taylor for helping me in writing this paper.

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Archives of Disease in Childhood 1992; 67: 731–736

Family characteristics and insulin dependent diabetes

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Abstract

During the calendar year of 1988 a survey of new cases of insulin dependent diabetes mellitus (IDDM) in children under the age of 15 years in the British Isles was conducted. After cases had been confirmed and permission obtained to contact the families, postal questionnaires were sent to the parents of children diagnosed in England, Wales, Northern Ireland, and the Republic of Ireland.

Children who developed diabetes were significantly more likely to be heavier at birth in comparison with national reference data. The diabetic children were less likely to have been breast fed, and there were more children than expected whose fathers were in non-manual occupations. Where there was a first degree relative with IDDM there were positive correlations between the age at diagnosis of the index cases and that of their diabetic fathers and their diabetic siblings, but not their diabetic mothers. A higher proportion of children than expected who were diagnosed under the age of 5 years had fathers with IDDM.

Characteristics of family members associated with IDDM in children that might provide pointers to the aetiology of the disease include heavier birth weight, method of infant feeding, the age at onset of IDDM in affected fathers and affected siblings, and the family lifestyle as defined by social class of the father.

Insulin dependent diabetes mellitus (IDDM) is currently viewed as resulting from environmental factors initiating progressive pancreatic islet cell destruction in genetically susceptible individuals.[1] As part of a survey of childhood onset diabetes diagnosed before the age of 15 years in the British Isles during 1988,[2] we documented characteristics of family members of the children concerned, seeking pointers to the aetiology of the disease. The analysis that follows relates to information obtained from postal questionnaires sent to the parents of the children.

Patients and methods

Ethical approval for this national study was obtained from the Bristol and Weston Health Authority and the British Medical Association, and the study protocol was scrutinised by the ethics advisory committee of the British Paediatric Association.

Permission to contact the families was sought from both the reporting paediatrician/physician and the family practitioner. Second and third reminders were sent to doctors if they did not respond to the first request. Questionnaires to the parents were sent two to three months after the diagnosis with a reply paid envelope for their return. If there was no response within one month, a second questionnaire was sent, with a final reminder if no response was forthcoming after a further one month. If a family had left the area, an attempt was made to contact them by obtaining the address of their new family practitioner from the local (then) family practitioner committee.

Special arrangements were made for the 190 children diagnosed in Scotland and the 75 children diagnosed in the Oxfordshire Regional Health Authority area where separate studies were ongoing (the Scottish Study Group for the Care of Young Diabetics[3] and the Bart's Oxford Family Study[4]). Questionnaires were not sent to the parents of children in these two areas in order not to prejudice the collection of data by local researchers. There was, however, information from the Bart's Oxford Family Study on family history of first degree diabetes and social class which was relevant to our study. Data were thus available on 1175/1410 (83%) families for family history, social class and age of mother at delivery (British Isles excluding Scotland), and on 1100/1335 families (82%) for birth weight and infant feeding practice. Complete statistics were not always available on every case, giving totals of <1175 for most analyses. Sources of information and families excluded from the study are shown in table 1.

Family history of IDDM was included in the analysis only for those cases where there was information on the biological parents or full siblings. Half siblings with IDDM were included in the analysis of the relationship between age of onset of an affected sibling and that of the index case. Step siblings, parents with diabetes that was not insulin dependent, and parents or siblings known to have developed diabetes after the diagnosis of the index case were excluded.

For diabetic children diagnosed in England and Wales, comparisons of birth weight (recalled by the mother) were made with birth weights of babies born in 1980, the mid-point of year of birth of our study population, available from national published data.[5] Comparisons of social class were made on 10 000 children who were part of the 1970 British Births Survey and still alive in 1980.[6] The latter study used the 1970 *Classification of Occupations*.[7] In our study, social class was based on the occupation (using

Table 1 *Sources of information*

Source	*No of reported cases <16 years*	*No of confirmed cases <16 years (% reported)*	*Study cases <15 years**
Paediatrician	1466	1435 (98)	1412
Physician	80	80 (100)	52
Specialist nurse/health visitor			
Paediatrician care	127	107 (84)†	104
Physician care	52	46 (88)†	27
General practitioner care	1	1	1
Mother	6	6	4
Total	1732	1675 (97)	1600
Excluded from questionnaires:		190 Scotland 75 Oxfordshire Regional Health Authority 2 Deaths 14 Refusals (by doctors)‡ 42 Non-responding general practitioners 3 Emigrations 20 Too late	
Total		346	
Cases sent questionnaires		1254 (78% of 1600)	
No of questionnaires returned		1100 (88% of 1254)	

*Original data collection on cases aged <16 years at diagnosis. study cases restricted to age <15 years at diagnosis; primary cases only
†By consultant paediatrician or physician
‡For example family bereavement, adverse social conditions.

the 1980 *Classification of Occupations*[8] together with educational qualifications) of the mother's partner at the time of diagnosis, regardless of whether or not he was the diabetic child's biological father. In order to reduce the bias introduced by changes in class composition between the 1970 and 1980 definition of classifications,[9] social class was aggregated into non-manual (I+II+IIINM) and manual (IIIM+IV +V) occupations. For breast feeding comparisons we used national data available from the Office of Population Censuses and Surveys (OPCS) collected on children born during 1980.[10] Maternal ages at the delivery of the diabetic children were compared with unpublished national data on maternal age (OPCS).

STATISTICS

Analyses were performed using the statistics packages SPSS and BMDP (for survival analysis[11]). Non-parametric tests were used, except where it was appropriate to use parametric tests. Methods for direct standardisation and confidence intervals were described in Armitage and Berry[12] and Kirkwood.[13]

Results

RESPONSE

Of the 858 reporting hospital doctors, 844 (98%) confirmed their newly diagnosed cases, and of 1301 family practitioners subsequently contacted 1259 (97%) responded. Questionnaires were returned by parents of 88% of the cases (1100/1254, or 69% of the original 1600 children).

Table 2 *Number (%) of children with IDDM* compared with children from OPCS† data grouped by birth weight singletons, England and Wales (z=standardised normal deviate)*

	Birth weight		
	≤2500 g	*2500–<4000 g*	*≥4000 g*
IDDM (1973–88)	65 (7)	783 (82)	104 (11)
OPCS (1980)	52 779 (6)	509 707 (86)	46 012 (8)

$\chi^2=16{\cdot}51$, p<0·001 (2df).
*Excludes children with IDDM mothers (n=21/22)
†Includes children with IDDM mothers

THE FAMILIES

From the questionnaires completed, there was information on 1091 mothers and 1072 fathers. There were 18 twin pairs: six identical (one of whom had previously developed IDDM), 10 not identical, one query, and one unknown; and one set of triplets.

ETHNIC ORIGIN

All the parents who responded completed the section on ethnic origin. Of the 1087 cases where full data were available for England and Wales, 1041 (95·8%) children were of European origin, 18 (1·7%) were of Indian subcontinent origin, five (0·5%) of African origin, and 23 (2·1%) of mixed origin. There are similar to the proportions from the British Births Survey: 96·7% white, 1·7% Indian subcontinent, 1·4% African, and 0·2% other (10 year follow up, unpublished data).

BIRTH WEIGHTS

The mean (SD) birth weight of 21 study children born to mothers who had themselves developed diabetes before their children (n=22, one birth weight not available) was not significantly different from that of the 1057 study children born to non-diabetic mothers (3600 (810) g compared with 3370 (560) g respectively; $t=1{\cdot}30$). However, the mean (SD) birth weight of 14/21 children (group A) whose mothers developed diabetes before the deliveries of the index cases was significantly less than that of 7/21 children (group B) whose mothers developed diabetes after their deliveries (3330 (780) g compared with 4140 (570) g; $t=2{\cdot}75$, p<0·02). The heavier birth weights of group B were not due to birth order (not significant by Fisher's exact test), an excess of males (not significant by Fisher's exact test), nor maternal age (Mann-Whitney, z=1·37). There was no relationship between birth weight and the diabetic status of the fathers (F=0·50), nor the children's age at diagnosis (Spearman's rank correlation coefficient, r=−0·054).

In order to compare the birth weights of the diabetic children with national data on singleton children born in 1980 only those study children who were singletons, resident in England and Wales, and whose mothers did not have insulin dependent diabetes at delivery were incuded. Birth weights were divided into three groups: <2500 g, 2500–<4000 g, and ≥4000 g, and the numbers of study children in each group were compared with the number of children similarly grouped by OPCS. There were more diabetic children in the heaviest group than expected ($\chi^2=16{\cdot}51$, p<0·001 (2df); table 2).

BREAST FEEDING

Of 1009 study children born in England and Wales where information was available, 556 were initially breast fed (55%). After using the method of direct standardisation to correct for mothers' education,[12] an important factor in the analysis of breast feeding, the adjusted proportion for the infants who were breast fed and subsequently developed diabetes was 58% (99% confidence interval 51% to 64%), which is significantly lower than the breast feeding proportion in the 1980 infant feeding study[10] of 67% (99% confidence interval 65% to 69%, $p<0{\cdot}01$). In order to remove any potential bias introduced by our question: 'Was the child breast fed?' being phrased differently from question in the infant feeding study: 'Did you ever put your baby to the breast (even if it was once only)?', further analyses were carried out which avoided the immediate postpartum period. Diabetic children and control children who had never been breast fed or breast fed for less than two weeks were grouped together and compared with children who had been breast fed for two weeks or longer; the result was significant ($\chi^2=9{\cdot}865$, $p<0{\cdot}01$, table 3). When the duration of breast feeding was divided into three categories: 2–<6 weeks, 6 weeks–<4 months, and ≥4 months, there were more study children than expected who had discontinued breast feeding at 2–<6 weeks ($\chi^2=14{\cdot}609$, 2df, $p<0{\cdot}01$, table 4). As breast feeding rates in England and Wales were low in 1975,[10] we reanalysed the data for the cases born 1978–82 (bracketing the 1980 control data); after correcting for mothers' education, the adjusted proportion for the study infants was 60% (99% confidence interval 57% to 64%, $p<0{\cdot}01$). However, the detailed analyses subdividing the postpartum period as above were not significant (division at two weeks of age: $\chi^2=0{\cdot}56$ and duration of breast feeding: $\chi^2=2{\cdot}08$).

FAMILY HISTORY OF DIABETES

There were 105/1175 (8·9%) study children with at least one first degree relative with IDDM. There were 41 (3·5%) affected fathers (nine diagnosed as having IDDM after the birth of the index case); seven fathers had diabetes that was not insulin dependent (all diagnosed before the birth). There were 22 (1·9%) affected mothers, seven of whom had IDDM diagnosed after the delivery of the index case; two mothers had diabetes that was not insulin dependent (all diagnosed before the delivery). There were 50 (4·2%) siblings with IDDM.

FATHERS AND MOTHERS WITH IDDM

Sixty two diabetic children had at least one biological parent with IDDM. The age at diagnosis of children with an affected parent was significantly less than that of children without an affected parent (median ages of children 5·8 years and 8·9 years respectively, Mann-Whitney, $z=2{\cdot}31$, $p=0{\cdot}02$). Using simple non-parametric statistical techniques, we found a significant relationship between the age at onset of affected parents and the age at onset of their diabetic children ($n=63$, Spearman's rank correlation coefficient $r=0{\cdot}445$; $p<0{\cdot}02$). When the 41 fathers and 22 mothers were considered separately the relationship was apparent only with the fathers ($r=0{\cdot}445$, $p<0{\cdot}01$ (fig 1); mothers: $r=0{\cdot}388$, not significant).

The associations with the child's age at diagnosis of paternal or maternal age at diagnosis could have been due simply to the amount of time that the parent had in which to develop diabetes. Older diagnosed children would have older fathers (or mothers), who may have developed the disease in later life; for children diagnosed younger this was not possible. Therefore survival analysis, using a Cox proportional hazards model,[11] was used to model the time during which the fathers' (or mothers') lives had been observed: from their birth until they or their children developed diabetes. The age at which the child developed diabetes was entered as a covariate, and was found to be a significant factor in the model for fathers but not for

Table 3 Breast feeding in children who subsequently developed IDDM, date of birth 1973–88, compared with national data (OPCS 1980[10]) (results are number (%) of children in each group)

	Breast fed		*Total*
	Never or <2 weeks	*≥2 weeks*	
IDDM (1973–88)	522 (52)	487 (48)	1009 (100)
OPCS (1980)	1731 (46)	2023 (54)	3754 (100)

$\chi^2=9{\cdot}865$, $p<0{\cdot}01$.

Table 4 Duration of breast feeding in children who subsequently developed IDDM, date of birth 1973–88, compared with national data (OPCS 1980[10]) (results are number (%) of children in each group)

	Duration of breast feeding			*Total*
	2–6 weeks	*6–12 weeks*	*>12 weeks*	
IDDM (1973–88)	147 (30)	134 (28)	206 (42)	407 (100)
OPCS (1980)	450 (22)	574 (28)	999 (50)	2023 (100)

$\chi^2=14{\cdot}608$, $p<0{\cdot}01$ (2df)

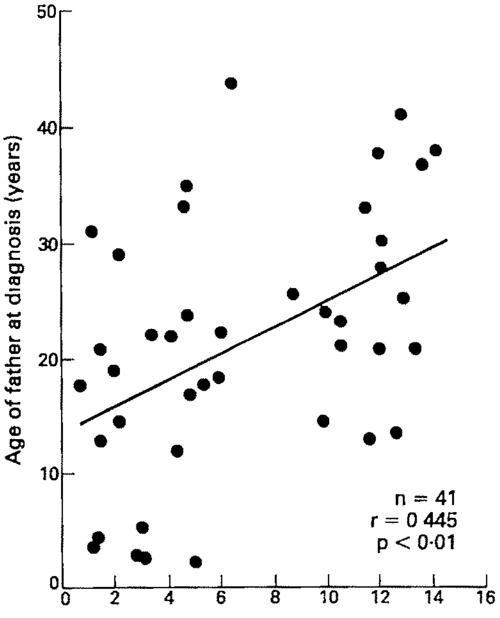

Figure 1 Relationship between age at diagnosis of 41 children with IDDM and that of their similarly affected fathers.

mothers (table 5). Thus we can say that the age at diagnosis of both father and child were associated, but this was not necessarily so for mothers.

If the index cases were divided into age groups 0–4 years and 5–14 years at diagnosis, a higher proportion of children than expected in the age group 0–4 years had fathers with IDDM (χ^2=10·54, p<0·005); there was no such difference in proportions for the children of mothers with IDDM (table 6).

SIBLINGS WITH DIABETES

There were 44 full siblings (one an identical twin) and six half siblings with IDDM who were diagnosed before the index case. Six siblings were diagnosed less than one year before the index case; all but three siblings were diagnosed under the age of 15 years. There was no difference between the age at diagnosis of study children with an affected sibling compared with that of those without (Mann-Whitney z=1·26). There was a positive correlation between the age at onset of diabetes in the index cases and that of their affected siblings (n=50, Spearman's rank correlation coefficient, r=0·316, p=0·03, fig 2).

The age at diagnosis of affected siblings was also considered using survival analysis to model the time over which the siblings' lives had been observed. The age at diagnosis of the study child was entered as a covariate and found to be a significant factor in the model (global χ^2= 15·63, 1df, p=0·0001): thus we can say that the age at diagnosis of both sibling and child were associated. When further survival analyses were carried out for cases with siblings of the same or different sex, the results were significant for same sex pairs (n=26, global χ^2=10·89, 1df, p<0·001), but not significant for different sex pairs (n=24, global χ^2=0·01, 1df).

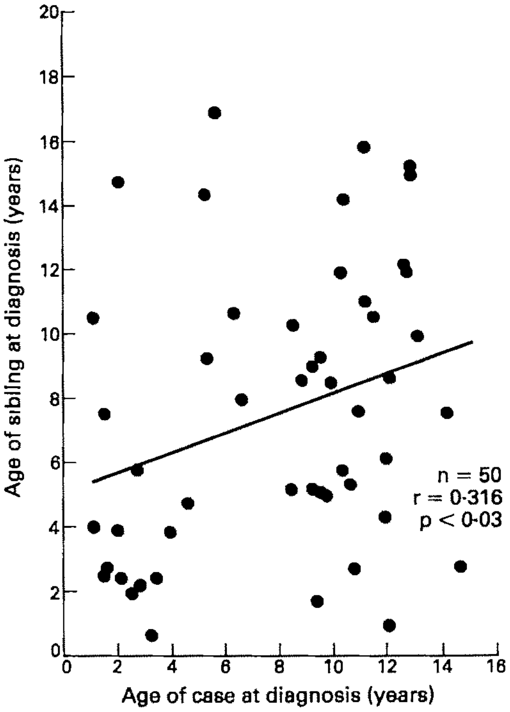

Figure 2 Relationship between age at diagnosis of 50 children with IDDM and that of their similarly affected siblings.

Table 5 Survival analyses of diabetic parents to investigate the relationship between parental age at diagnosis and child's age at diagnosis (age of child was entered as a covariate: its significance relates to the p value)

Diabetic parent	*No of diabetic pairs*	*Global χ^2*	*p Value*
Mothers+fathers	63	13·44	0·0002
Fathers	41	10·22	0·001
Mothers	22	3·24	NS

Table 6 Number (%) of children aged 0–4 years and 5–14 years at diagnosis with fathers and mothers with IDDM

	Age at diagnosis		
	0–4 years	*5–14 years*	
Father.			
With IDDM	20 (7)	21 (2)	χ^2=10·54
Without IDDM	279 (93)	840 (98)	p<0·005
Total	299 (100)	861 (100)	
Mother			
With IDDM	7 (2)	15 (2)	χ^2=0·68
Without IDDM	293 (98)	848 (98)	NS
Total	300 (100)	863 (100)	

Table 7 Social class of fathers of diabetic children compared with fathers of children from the British Births Survey followed up in 1980 (unpublished data) (results are numbers (%) of children in each group)

	Social class		*Total*
	Non-manual	*Manual*	
IDDM (1973–88)	509 (55)	419 (45)	928 (100)
British Births Survey (1980)	4353 (40)	6572 (60)	10 925 (100)

χ^2=79·00, p<0·001.

SOCIAL CLASS

There were higher proportions than expected of diabetic children whose fathers were in non-manual occupations compared with children in the British Births Survey followed up in 1980 aged 10 years (unpublished data) (table 7).

AGE OF MOTHERS AT DELIVERY OF INDEX CASE

From 1973–88, the mean age at delivery of the mothers of the diabetic children was significantly higher than that of mothers in the general population (OPCS, unpublished data, n=16 years, Wilcoxon matched pairs test T=7·5, p<0·01).

Discussion

It was not possible to quantify any bias in the analyses that may have been introduced by not contacting the parents of children diagnosed in Scotland or the Oxfordshire Health Authority, nor to evaluate any differences in family characteristics between the parents who responded to the questionnaire and those who did not. With these reservations in mind, analyses based on questionnaire information nevertheless suggest that certain characteristics of diabetic children and their families distinguish them from non-diabetic groups.

The birth weight of the diabetic children was greatest in the seven cases where the mother herself developed diabetes after the delivery, indicating perhaps the early stage of the maternal diabetogenic process. The 14 children born to mothers with established IDDM were of normal birth weight, presumably reflecting carefully monitored pregnancies. There were more children who developed IDDM in 1988 than expected weighing more than 4000 g at birth (11% of cases) compared with national birth weight data (8% of the population). How birth weight might relate to the subsequent development of diabetes is not clear, but it is interesting to note that adult males with impaired glucose tolerance or newly diagnosed diabetes appear to have been of lower than average birth weight.[14] Could the pattern of intrauterine growth influence or reflect the long term function of the immune system?

Children who subsequently developed IDDM were less likely to have been breast fed in infancy compared with the children in the 1980 infant feeding study. Because of the differences in the way the two sets of data were collected, the results must be confirmed with case-control data before they can be accepted with any confidence. Nevertheless, our lower proportion is in agreement with other researches,[15–17] and supports the proposal that breast feeding affords some protection against the development of diabetes. Researchers in Finland, where the incidence of diabetes in childhood is the highest in the international league, found that newly diagnosed children (mean age 9·1 years) had significantly higher concentrations of IgA antibodies to cows' milk compared with age matched controls.[18] This suggests a link between the initiation of the diabetogenic process, and the reciprocal effects of an antigenic challenge of cows' milk protein and the reduction in gastrointestinal immune defence available from breast milk.[19]

It has been shown that the risk of developing diabetes for children of fathers with IDDM (4%–6%) is greater than for children of mothers with IDDM (2%–3%).[20 21] In our study, the number of affected fathers was almost double that of affected mothers (41:22), there were more chidren than expected aged 0–4 years at diagnosis with an affected father, and there was a significant relationship between the age at diagnosis of children with IDDM and the age at diagnosis of their affected fathers. The last finding is not dissimilar to the pattern noted in Huntington's disease, in which fathers diagnosed young produce children diagnosed young; moreover, as in our study, a significant relationship exists between age at diagnosis of affected sibling pairs.[22] We did not, however, observe that a stronger correlation existed in mother-child pairs compared with father-child pairs, as in Huntington's disease, but the number of mothers with diabetes is small. It has previously been noted the mothers of diabetic children are older at delivery than mothers of control children,[19 23] and the mean age at delivery of the mothers of our cases was greater than that of mothers in national studies.

Compared with national data, a higher proportion of diabetic children than expected came from families in which the father's occupation was classified as non-manual. Non-responding parents (154/1254, 12%) would have included a number of fathers with manual occupations, who may have been less willing or less able to complete a questionnaire, thus introducing bias into our data. Nevertheless, even if these 154 families were all included in the manual group and the analysis repeated, the results still indicate a significantly greater number of children with diabetes who have fathers in non-manual occupations ($\chi^2=27{\cdot}90$; $p<0{\cdot}001$). In two local studies in England the prevalence of IDDM in children has been shown to be significantly over-represented in social class I.[24 25] In a study from Montreal incidence rates for IDDM in children aged 0–14 years were higher in wealthier neighbourhoods than in poorer ones.[26] In contrast, a study in Denmark showed that incidence rates for children aged 0–14 years in Copenhagen county were twice as high in the southern poorer area than in the northern more prosperous area.[27] A Swedish study demonstrated a higher proportion of fathers in manual occupations compared with a control population,[28] and a recent study from the north of England suggests that diabetes is more common in families who are socially deprived.[29] We found a high incidence of childhood diabetes in the Northern region and Wales among children with unemployed fathers. These diverse and apparently conflicting results illustrate the difficulty of analysing data based on the social class of the father (or father figure), which takes no account of the mother's occupation or family income and leaves fatherless children in an 'unclassified' category. To clarify these relationships a case-control study will be necessary using more refined measures to define differences in the domestic scene, such as diet[30 31] and the frequency of viral infection,[32] which may contribute to the aetiology of diabetes.

We have defined certain characteristics of family members associated with IDDM in children. These include birth weight and the method of infant feeding, the age at onset of IDDM in affected fathers and affected siblings, and the family lifestyle as defined by social class of the father. A case-control study will be necessary to quantify the risks associated with such variables: this we are undertaking as part of a further national study of childhood onset IDDM in the British Isles.

This study was supported by the British Diabetic Association and the then Nordisk-UK. We should also like to thank for their collaboration the British Paediatric Surveillance Unit (which is supported by a grant from the Children Nationwide Medical Research Fund), all the paediatricians, physicians, and nurses for reporting cases, Professor J Jarrett, Professor J Golding, and Dr EAM Gale (Bart's Oxford Family Study) for their generous help and cooperation, Mrs M Pears and Miss K Birmingham for help with coding the questionnaires, Mrs J-A Evans and Miss R Greenwood for statistical advice, and all the parents who completed the questionnaires

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Archives of Disease in Childhood 1992; 67: 737–740

IgG antibodies in early *Pseudomonas aeruginosa* infection in cystic fibrosis

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Accepted 5 March 1992

Abstract

The relationship between IgG antibodies to *Pseudomonas aeruginosa* and its isolation from sputum was determined in 100 patients with cystic fibrosis observed at intervals of two months for a median period of one year. Only one patient had a raised antibody titre (>22·9 ELISA units) before isolation of *P aeruginosa*. Initially 65 patients were antibody negative, of whom 48 were also culture negative. Of 24 patients with positive sputum culture and negative antibodies, seven became antibody positive at a median (range) 15 (6–25) months later. The remaining 17 patients continued antibody negative until the end of the study at a median range 15 (1–123) months after becoming culture positive. This latter group were younger and had more intermittently positive sputum cultures. In general positive IgG antibody titres do not predate isolation of *P aeruginosa*, but in some patients are present soon after acquisition of infection. A positive titre indicates significant exposure to *P aeruginosa* and could be used to detect infection in patients unable to produce sputum and possibly indicate the effect of early antipseudomonal treatment.

Serum IgG antibody titres to *Pseudomonas aeruginosa* may be a sensitive and early indicator of the colonisation of the lungs with this organism in patients with cystic fibrosis.[1,2] It has been reported that antibody titres are raised before isolation of *P aeruginosa* from sputum and that antibody titres may fall after antibiotic treatment at this early stage of infection.[2,3] *P aeruginosa* infection of the chest in cystic fibrosis is the major determinant of survival in older children and adults.[4] Once established in the airways, as indicated by regular isolation from sputum, *P aeruginosa* is extremely difficult to eradicate with antibiotic treatment. The detection of serum antibodies might be a means of early diagnosis of the presence of the organism in the respiratory tract, which would allow early antibiotic intervention with partial or complete eradication of the organism at this time, although such recommendations are based on limited data.[5,6]

We examined the relationship between the serum anti-*P aeruginosa* IgG antibody titres and the presence of organisms in the sputum cultures of patients with cystic fibrosis.

Patients and methods

PATIENTS

Patients were recruited from the adult and paediatric cystic fibrosis clinics at Nottingham City Hospital based on their willingness to give regular blood and sputum samples. One hundred patients from a total of 130 agreed to take part and were studied prospectively. Samples for *P aeruginosa* antibody measurement were either serum samples from venepuncture blood samples or whole blood spots, collected directly onto Guthrie cards from a finger puncture. Such samples are interchangeable in our assay.[7]

Blood and sputum samples were collected at approximately two monthly intervals from a range of patients with cystic fibrosis, who were categorised into chronic, intermittent, or negative for *P aeruginosa* infection on the basis of sputum cultures. Patients were considered to have chronic infection if *P aeruginosa* was isolated on three or more occasions during a 12 month period, and intermittent infection was defined as any isolation in the year before the study or one or two isolations during any 12 month period during the study. The study had ethics committee approval.

ASSAYS

Specific IgG antibody to *P aeruginosa* was determined in an antibody capture enzyme linked immunosorbent assay (ELISA).[7] Soluble antigens, prepared from *P aeruginosa* serotypes 01–17 of the International Antigenic Typing Scheme, were used to coat microtitre plates.[8] Gelatin was used to block areas of the plate where the antigen had not adhered. After incubation with diluted serum or blood spot eluates, biotinylated antihuman IgG was used to probe for the captured antipseudomonal antibodies. This was followed by avidin peroxidase and peroxidase substrate to give a colour signal. This reaction was stopped with sodium hydroxide and absorbance read at 455·5 nm.

CALCULATIONS

On each plate, four wells were left without coating antigen and, after blocking, were exposed to a pooled control, low *P aeruginosa* antibody titre serum to quantify non-specific binding to IgG. A high titre *P aeruginosa* antibody serum was used as reference, each unknown sample was expressed in ELISA units (EU), which was calculated as a percentage of this value after subtracting the non-specific binding optical density (OD, the mean of the low control wells) from both.

$$\text{Unknown sample EU} = \frac{\text{Unknown OD} - \text{low control OD}}{\text{High control OD} - \text{low control OD}}$$

Intra-assay and interassay variation was determined from eight replicates per plate of two blood spot eluate samples.

STATISTICAL METHODS

Data from the control subjects was non-normally distributed and was log transformed to calculate the mean and SD. The mean + 1·96 SD was taken as the upper limit of antibody concentration in controls. Other non-normally distributed data is expressed as median and non-parametric confidence interval or range if stated.[9] For paired comparisons differences were normally distributed and were analysed by Student's *t* test; $p<0·05$ was accepted as indicating a significant difference.

Results

(1) CONTROLS

A normal range was determined from 32 healthy adults and children of a similar age range to the patients with a mean (+1·96 SD) of 5·3 (22·9) EU. Mean interassay variation was 8·6% and intra-assay variation 7·1% (coefficient of variation).

(2) PATIENTS

Over a study period of three years 100 patients were monitored for a median period of 1·0 year. Median age at entry was 11·3 years (range 2 months–23 years) and the median number of samples per patient was four (range 3–5).

At entry to the study

Initially 34 patients had *P aeruginosa* cultured from their sputum and a positive antibody titre (group I, fig 1). Seventeen patients were culture positive but antibody titre negative (group II) and one was culture negative and antibody positive (group III). Forty eight patients were both culture and antibody negative (group IV, table).

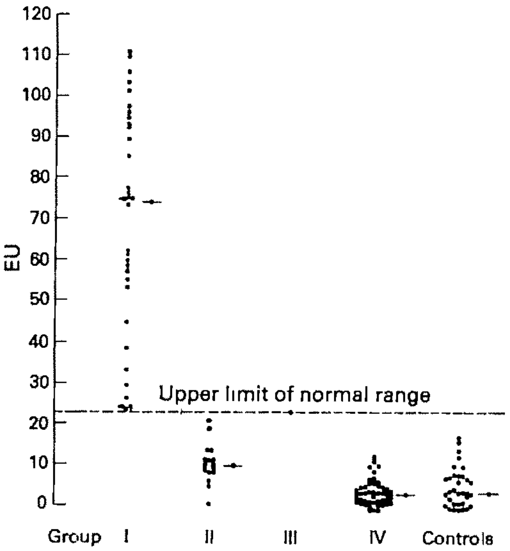

Figure 1 Individual ELISA values for all patients in the study at entry. Patients are grouped according to their antibody titre and culture characteristics. The median for each group is shown

Changes occurring during the study

During the study group I patients showed no significant change in antibody titres (70·7 EU *v* 79·2 EU, mean difference 2·4 EU, p=0·5). The effect of acquisition of *P aeruginosa* and the subsequent antibody response was sought in the group IV patients who were initially culture and antibody negative. Of these 48 patients 39 remained in group IV and showed no change in antibody titres (4·5 EU *v* 3·4 EU, mean difference 0·6 EU, p=0·37). The remaining nine patients changed their status during the study: seven cultured *P aeruginosa* from their sputum but remained antibody negative: one patient became culture and antibody positive simultaneously and one became antibody positive before becoming culture positive. This gave a total of 24 patients exhibiting a group II pattern (seven from group IV and 17 initially in group II) during the study. Of these 24 patients seven became group I patients when positive antibody titres developed, however, there was a median lag period of 15 months (range 6–25 months) from first culture to a positive titre. Of these

The distribution of patients in groups I-IV based on their antibody titre and culture characteristics at entry to the study. Chronic and intermittent culture of P aeruginosa is also shown

Positive sputum culture.	
Positive IgG titre (group I) (n=34:33 chronic, 1 intermittent)	Negative IgG titre (group II) (n=17. 7 chronic, 10 intermittent)
Negative sputum culture.	
Positive IgG titre (group III) (n=1)	Negative IgG titre (group IV) (n=48)

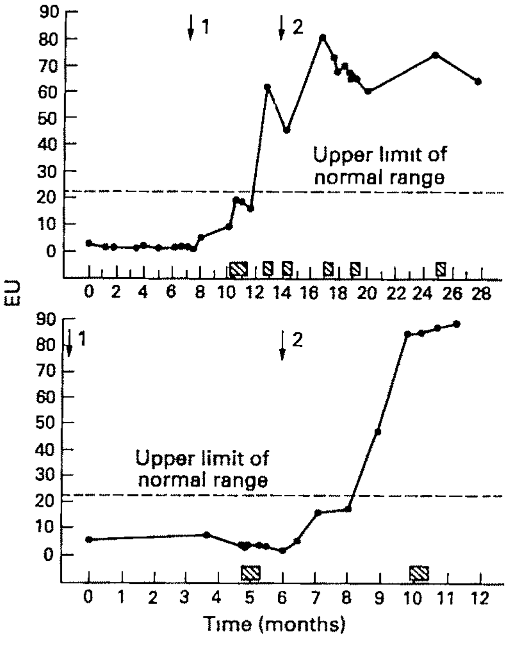

Figure 2 The pattern of antibody titre changes in two representative patients; (1) is the first time P aeruginosa was cultured and (2) is the time culture became chronic Hatched areas represent periods of antipseudomonal antibiotic treatment

seven patients, five were chronically culturing *P aeruginosa* from the sputum and two were only intermittently isolating this organism. The remaining 17 patients with positive sputum culture (group II) have not yet shown an antibody response; median time from first culture of *P aeruginosa* to the end of the study was 15 months (range 1–123 months). These 17 patients tended to be younger than the other seven patients making up the 24 with group II features (median (range) of 8·5 (1·0–24·8) years *v* 14·6 (5·2–19·3) years). Six of this subgroup of patients were chronically isolating *P aeruginosa* and 11 were intermittently isolating this organism from their sputum. Initially only one of the 100 patients studied had positive antibody titres with negative sputum cultures (group III), although a positive sputum culture was documented 13·2 months after the first positive serum result. During the study one other patient met group III criteria for six months before becoming both antibody titre and culture positive. In patients infected with *P aeruginosa* and later developing antibodies there was some variability of the antibody titre during the rising phase, but such changes were unrelated to anti-pseudomonal antibiotic treatment. Examples of the pattern of antibody development in two patients are given in fig 2.

Discussion

In our study 24 patients developed positive sputum cultures for *P aeruginosa* before the development of a positive antibody titre, whereas only two patients showed a positive IgG titre preceding isolation of *P aeruginosa* from their sputum. In a single patient antibodies became positive at the same time as sputum culture. One third of the patients with a delayed response became antibody positive between six and 25 months after the first isolation of *P aeruginosa* from their sputum by which time most were chronically infected. The remainder had not developed an antibody response by the end of the study, although one to 123 months had elapsed from the first isolation of *P aeruginosa*. The median follow up period of this group was only 15 months and more patients may have become antibody positive with a longer period of observation. Those without positive antibodies by the end of the study tended to be younger and had more intermittent infections, which could explain their longer lag period. They may have been more effective at clearing bacterial products from the respiratory tract than older patients who may have more accumulated lung injury and poorer airways clearance.

Our findings contrast with an earlier report that IgG antibodies to *P aeruginosa* may predate isolation of the organism from sputum.[2 3] This may be due to differences in the frequency of sampling, the assay methods used, or the microbiological facilities available in the two centres. A major difference from the methods used in our study was the use of whole bacterial cell antigens derived from seven local strains which represented 85% of isolates of *P aeruginosa* in their patients over a six month period.[2 3] Each antigen was used independently to coat assay wells and the results from the seven determinations per sample were accumulated to derive an antibody titre. The normal range for their assay was derived from 17 patients with other conditions. No intra-assay and interassay variation or other performance characteristics of the assay were quoted. In our assay a soluble extract of 17 standard serotypes containing 64 antigens was used.[8] We used 32 healthy subjects to define a control range for antibody values. This gave a wide allowance for variation of antibody titres within this population, although the choice of such a cut off is fairly arbitrary and not directly comparable with other assay systems and healthy populations. It is possible that increases in antibody titre occurring before isolation of *P aeruginosa* from the sputum, that have been reported by Brett *et al*,[2 3] may be due to variation within the true normal range. An increased frequency of sampling would have helped to determine whether this was so and would have given a better defined profile for their patients. In addition, we were also unable to demonstrate clearcut reductions in antibody titres after antibiotic treatment in the period after acquisition of infection. This might be expected, because a fall in antibody titre is only likely to occur after the long term eradication of *P aeruginosa*, which seldom happens with traditional antibiotic regimens.[5]

It was hoped that detection of antibodies before sputum culture became positive would allow the detection of infection, particularly in children too young to produce sputum samples, and could be used as an indicator of early infection at a time when aggressive anti-pseudomonal treatment might be beneficial.[5 6] IgA antibodies may be a better indicator of early infection.[10 11] A negative antibody titre in the presence of either chronic or intermittent isolation of the organism from sputum is difficult to interpret and is of no management value in patients unable to provide sputum. Absence of an antibody response in patients isolating the organism from their sputum may represent a period of less active injury, possibly because of a less intense host immune response or partly be due to better airway clearance mechanisms.

A positive titre of IgG antibody indicates a significant degree of exposure to *P aeruginosa*, however, even if sputum culture is negative, intermittently positive, or unavailable. In this situation, specific antibiotic treatment could sensibly be instituted, particularly if there was a deterioration in respiratory function. This approach may be particularly applicable to children where early treatment of *P aeruginosa* may reduce the rate of lung destruction, although more studies are needed to demonstrate any long term benefits.[5 6] Combination of our assay system and bloodspot sampling provides a means of monitoring *P aeruginosa* acquisition in children from an early age.

JSE and RJR were Cystic Fibrosis Research Trust Clinical Fellows and SMC was supported by the Cystic Fibrosis Research Trust

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Food and stimulation are good for children

It is my purpose to draw your attention to an article published in the *Lancet* on 6 July 1991 (Grantham-McGregor *et al, Lancet* 1991;**338**:1–5). This paper describes research into the nutrition of stunted children in Jamaica. A house to house survey in Kingston identified 127 poor, undernourished, stunted children aged between 9 and 24 months all of whom were more than 2 SDs below the mean for height. These poor, deprived, undernourished children were allocated to four groups.

The first group were given no extra food or stimulation but they were visited once a week. The research workers considered giving this group a placebo but it was considered unethical to give them a low energy supplement, so they were given nothing. The second group were given extra psychosocial stimulation. That is, the mothers were taught how to play with their children and given toys for the purpose. The third group were given extra food and the fourth, both food and stimulation.

After two years those given nothing had deteriorated as regards developmental quotient. The groups given supplementation or stimulation alone showed modest benefit, and the group given both supplementation and stimulation showed clear benefit. Twelve months into the study the measurements of developmental quotient showed the control group to have deteriorated considerably but the study was continued for another year.

So feeding poor, deprived, undernourished children is good for them and giving them a more stimulating environment is also good for them. I thought you'd like to know that.

ARCHIVIST

Archives of Disease in Childhood 1992; 67: 741–744

CONTROVERSY

The value of proximal small intestinal biopsy in the differential diagnosis of chronic diarrhoea

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Abstract

The value of proximal intestinal mucosal biopsy was reviewed in 381 children presenting with chronic diarrhoea over an eight year period. An enteropathy was detected in 44% of cases and was more frequently seen in those aged less than 6 months. A diagnosis was established in 91% of cases. The most common diagnosis was the postenteritis syndrome where the presence of an enteropathy indicated those requiring treatment with a cows' milk free diet. Other conditions where a biopsy facilitated diagnosis or treatment included giardiasis, enteropathogenic *Escheriichia coli*, crytosporidiosis, autoimmune enteropathy, and microvillous atrophy.

Coeliac disease was considered in 55% of children and established in 8%, clearly identifying those requiring a gluten free diet. This also emphasises the important role of the biopsy procedure in the exclusion of specific diseases.

Proximal small intestinal mucosal biopsy is an essential investigation in children with chronic diarrhoea in whom an enteropathy is suspected.

Diarrhoea is a major cause of morbidity and mortality in children throughout the world.[1] The advent of oral rehydration therapy represents a major advance in the management of acute diarrhoea.[2–4] However, this does not resolve the problem of chronic diarrhoea, which represents a difficult diagnostic problem because of the many causes that can be considered to be responsible for the illness.[5] The approach at Queen Elizabeth Hospital for Children is to perform a proximal small intestinal mucosal biopsy as a differential diagnostic procedure in children with chronic diarrhoea in whom an enteropathy is suspected. The aim of this paper is to assess the value of such an approach.

Patients and methods

The patients reviewed in the study were those presenting at Queen Elizabeth Hospital for Children between January 1982 and December 1989 with chronic diarrhoea (duration at least 14 days) who underwent proximal small intestinal mucosal biopsy.

The investigative procedure for these patients included an initial clinical assessment followed by routine microbiological, haematological, and biochemical analyses. Microbiological examination of the stools comprised negative staining electron microscopy for gastrointestinal viruses and light microscopy for ovas, cysts, and parasites. Bacterial culture was performed in order to identify salmonella, *Escherichia coli*, and shigella. After obtaining informed consent the children were fasted overnight, sedated, and a proximal small intestinal mucosal biopsy specimen obtained using a paediatric twin port biopsy capsule.[6] Histology, morphometry,[7] biochemistry,[8] and ultrastructure[9] of the small intestinal mucosa were studied depending on the specific clinical requirements. Duodenal juice was examined for the presence of *Giardia lamblia*. The histological report for each biopsy specimen was reviewed and, for the purposes of this study, graded into normal histology and mild, moderate, or severe enteropathy.[10] This grading depends mainly on the villous height and crypt depth. Discrete abnormalities such as those associated with lymphangiectasia were included in the normal group as the villous height and crypt depth were normal.

Patients with cows' milk sensitive enteropathy and postenteritis enteropathy were considered together as the diseases may coexist and are difficult to separate without resorting to food provocation and serial small intestinal biopsies.[11]

Results

During the eight year period 414 children presented with chronic diarrhoea and underwent proximal small intestinal mucosal biopsy. The notes of 381 were retrieved and reviewed retrospectively.

Two hundred and forty two of the patients (64%) were aged less than 2 years, 78 (20%) were between 2 and 5 years old, and the remainder (n=61, 16%) ranged up to 15 years of age. The male to female ratio was 1·4 : 1 (223 : 158). Coeliac disease was considered as part of the differential diagnosis in 210 of the children.

Two hundred and twelve children (56%) had a normal villous height and crypt depth (fig 1); 169 (44%) had an enteropathy, which was mild in 97 (25%) (fig 2), moderate in 38 (10%) (fig 3), and severe in 34 (9%) (fig 4). Enteropathy was more frequent ($p<0{\cdot}01$) in those aged <6 months (occurring in 76% 41/54) and less frequent ($p<0{\cdot}01$) in those aged more than 5 years (occurring in 25%, 16/61); analyses by χ^2 test.

In the group with normal histology (fig 1)

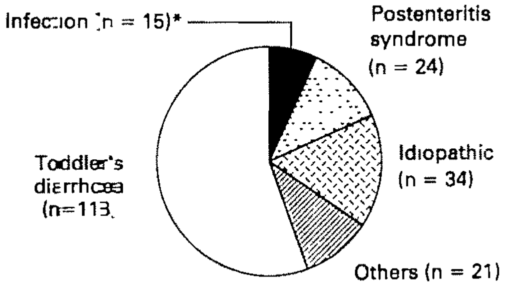

*Figure 1 Diagnoses of 212 children with normal histology. *For the 15 children with infection the infecting organisms were: salmonella (n=2), G lamblia (n=5), enteropathogenic E coli (n=4), aeromonas (n=3), and campylobacter (n=1).*

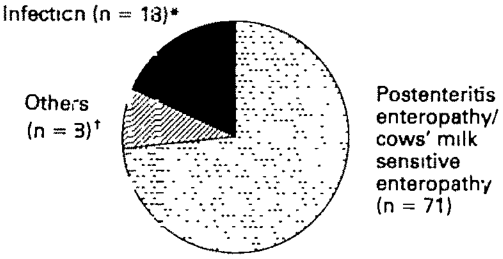

*Figure 2 Diagnoses of 97 children with mild enteropathy. *For the 18 children with infection the infecting organisms were: G lamblia (n=5), cryptosporidium (n=5) cryptosporidium + G lamblia (n=1) enteropathogenic E coli (n=4), campylobacter (n=1), and mixed bacteria (n=2) †The other eight children had inflammatory bowel disease (n=3), coeliac disease (n=2), intractable diarrhoea of infancy (n=2), and idiopathic intestinal pseudo-obstruction (n=1).*

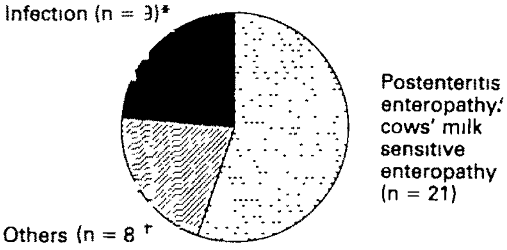

*Figure 3 Diagnoses of 38 children with moderate enteropathy. *For the nine children with infection the infecting organisms were: G lamblia (n=5), cryptosporidium (n=2), enteropathogenic E coli (n=1), and mixed bacteria (n=1). †The other eight children had intractable diarrhoea of infancy (n=2), autoimmune enteropathy (n=2), inflammatory bowel disease (n=1), allergic enteropathy (n=1), coeliac disease (n=1), and congenital microvillous atrophy (n=1).*

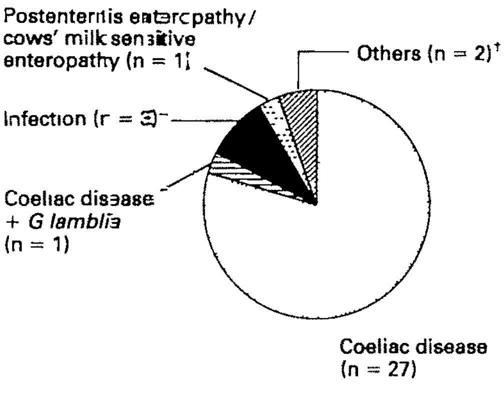

*Figure 4 Diagnoses of 34 children with severe enteropathy. *The infecting organism for all three children was G lamblia. †The other two children had intractable diarrhoea (n=1) and autoimmune enteropathy.*

toddler's diarrhoea was the commonest diagnosis (118/212, 56%). Twenty four cases (11%) were associated with the postenteritis syndrome, that is acute onset of diarrhoea persisting for more than 14 days, with or without failure to thrive. Of these 23 (96%) remained on a normal diet with spontaneous resolution of diarrhoea. In 15 patients (7%) bacteria or parasites were demonstrated. Other diagnoses were: food allergy (n=4), cystic fibrosis (n=3), IgA deficiency (n=3), sucrase-isomaltase deficiency (n=2), secondary lactase deficiency (n=2), glucose-galactase malabsorption (n=1), lymphangiectasia (n=1), ileal stricture (n=1), Shwachman's syndrome (n=1), nodular lymphoid hyperplasia (n=1), eosinophilic gastroenteritis (n=1), and inflammatory bowel disease (n=1). No diagnosis was established in 34 children with a normal mucosa (16% or normal histology group, 9% of total cases).

Postenteritis enteropathy or cows' milk sensitive enteropathy was the commonest diagnosis associated with mild histological changes (n=71, 73%; fig 2). In 18 (19%) cases pathogens, including *G lamblia*, cryptosporidium, campylobacter, and enteropathogenic *E coli*, were demonstrated. Other diagnoses included coeliac disease, inflammatory bowel disease, and idiopathic intractable diarrhoea of infancy. The patients with coeliac disease were biopsied on gluten challenge in order to establish the diagnosis after an empirical trial of a gluten free diet at another hospital.

Postenteritis enteropathy or cows' milk sensitive enteropathy was also the commonest diagnosis associated with moderate histological changes (n=21, 55%; fig 3). In nine (24%) cases pathogens were demonstrated and in eight (21%) cases other causes were established.

Severe enteropathy was associated with coeliac disease in 27/34 cases (79%), giardiasis in three (9%), and coeliac disease with giardiasis in one (3%). Other diagnoses included autoimmune enteropathy, the intractable diarrhoea of infancy syndrome, and the postenteritis syndrome (fig 4).

A total of 20 cases of giardiasis were identified. In 14 cases the parasite was identified by light microscopical examination of duodenal juice and/or small intestinal mucosa and was not seen in stool samples. In three cases giardia was found only in stool samples.

Discussion

Proximal small intestinal mucosal biopsy affords the demonstration of diffuse, but not discrete, abnormalities,[12] and in this series 44% of cases had an enteropathy identified. This alone serves to indicate its importance in paediatric gastroenterology. Its practical value resides not only in its ability to provide differential diagnostic information (when used in conjunction with clinical and laboratory procedures), but also to exclude diagnoses. For example, a diagnosis of toddler's diarrhoea is generally reached on clinical grounds.[13] However, the patients described here (representing a minority of the total referrals with toddler's diarrhoea during the study period) were suspected of having an enteropathy due to coeliac disease or cows' milk protein intolerance. After the demonstration of a normal small intestinal mucosa on a normal diet the diagnoses associated with the presence of an enteropathy were excluded. Similarly although no cause was found to explain the symptoms in 9% of cases, the biopsy procedure allowed many gastrointestinal diseases to be excluded.

A diagnosis was established in 91% of cases. The commonest diagnosis was the postenteritis syndrome in 117 (31%). In 24 children a normal mucosa was demonstrated and 23 were continued on a normal diet with resolution of the diarrhoea—that is, the biopsy influenced management with a successful outcome in all but one case. Seventy patients had mild, 21 had moderate, and one had severe histological changes. These children were placed on cows' milk free diets with immediate clinical benefit and several months later a carefully controlled milk challenge was performed in hospital. Most cases were able to tolerate a milk containing diet by the age of 2 years. Thus, the presence or absence of histological changes has helped to indicate which patients with the postenteritis syndrome require treatment with a milk free diet.

In 46 cases pathogens were demonstrated. *G lamblia* was identified in 20 (43%) and indicated treatment with metronidazole. Proximal small intestinal mucosal biopsy was a more effective method for the detection of *G lamblia* than stool microscopy.[14] One patient who did not improve after metronidazole treatment had further biopsies that established the additional diagnosis of coeliac disease. This underlines the value of the procedure in the differential diagnosis of chronic diarrhoea.

Enteropathogenic *E coli*, when identified adhering to the mucosa, were treated with appropriate antibiotics.[15] The finding of cryptosporidium explained the presence of an enteropathy[16] and indicated that therapeutic intervention would be ineffective. In all cases the diarrhoea resolved spontaneously.

Only 8% of the patients coming to biopsy had coeliac disease, even though it was considered as part of the differential diagnosis in the majority of cases. Thus a major role of the biopsy procedure is to exclude the presence of coeliac disease and thereby avoid the pitfalls of empirical treatment. As treatment of coeliac disease is for life it is crucial that the diagnosis is substantiated.

Other diagnoses associated with a severe enteropathy included autoimmune enteropathy,[17] congenital microvillous atrophy,[18] and the idiopathic intractable diarrhoea of infancy syndrome. A small intestinal biopsy is required for the diagnosis of microvillous atrophy and has allowed this discrete disorder to be recognised as part of the differential diagnosis of the intractable diarrhoea of infancy syndrome,[18] along with autoimmune enteropathy.[17] Indeed, proximal small intestinal biopsy has facilitated the evaluation of therapeutic trials in these diseases.[19–21]

In conclusion, we have reviewed the use of proximal small intestinal mucosal biopsy in children presenting with chronic diarrhoea. The routine performance of this procedure has established different diagnoses within the umbrella of chronic diarrhoea and influences management.[15–18] In experienced hands it is a simple and safe procedure and is an essential investigation in chronic diarrhoea.

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Commentary

This paper comes from a department which has set standards for paediatric gastroenterologists so its conclusions must be treated with respect. Children with diarrhoea lasting more than 14 days, in whom an enteropathy was suspected, underwent small intestinal mucosal biopsy. The authors conclude that this investigative technique is *essential* in such children.

Apart from providing an interesting insight into the spectrum of chronic diarrhoeal disease as experienced in east London, what message does this paper hold for general practitioners and general paediatricians who, elsewhere in the country, treat the bulk of such patients?

Unfortunately we are not told the population base from which the study group originated, nor the routes of referral, nor do we learn how the children in whom an enteropathy was suspected were differentiated from those in whom it was not. Presumably the grounds were clinical and this decided whether or not to perform a small intestinal mucosal biopsy. It would have been instructive to know how accurate was clincal impression, particularly as we learn that the authors considered coeliac disease in 55% and confirmed this diagnosis in 8%.

We cannot know, of course, what proportion of children who were not biopsied had an enteropathy. These children presumably lost their symptoms, which begs the question of how many of the biopsied children would have become asymptomatic without treatment.

Thus, the fact that 44% of children had an abnormal small intestinal mucosal biopsy specimen does not prove the procedure was necessary. One does not perform skin biopsies on children with eczema nor lung biopsy on those with lobar pneumonia even though they would be abnormal. The clinician treats the condition and anticipates improvement; if this does not occur then, of course, he might need to investigate further.

Of course if the enteropathy is likely to be longstanding or permanent—as in coeliac disease—or if the clinical picture is confusing and disturbing, the need for small intestinal mucosal biopsy is not disputed. The timing is crucial: in our, admittedly favoured, part of the country general practitioner or self referral of a child with diarrhoea of two weeks' duration is extremely unusual unless emergency admission had been sought because of anxiety about dehydration. Many general practitioners would have observed the effect of a cows' milk free diet first. Are they to be deprived of that option in the way that they are, rightly, strongly discouraged from experimenting with a gluten free diet?

Biopsy evidence permitted patients with toddler's diarrhoea, postenteritic syndrome, and cryptosporidiosis to avoid a period of cows' milk restriction but we question whether this justifies widespread adoption of the recommendations of the authors. Certainly, there were 14 cases of giardiasis not diagnosed by stool analysis (although three cases were missed on biopsy and duodenal aspiration). It would have been interesting to know whether any of those not biopsied had giardia infection and whether this diagnosis would have been entertained had their diarrhoea persisted and whether it would have been picked up by repeated stool sampling.

Jejunal biopsy is a very safe and not too distressing procedure in skilled hands,[1] although complications such as haemorrhage and small bowel perforation have been described.[2] Would it be as safe outside gastroenterological centres of excellence? Radiation protection regulations now demand, by statute, that individuals carrying out the procedure under fluoroscopic control must have attended a training course and acquired the necessary certification.[3] The presence of a radiologist in the department does not confer exemption. In small hospitals, therefore, it is likely that consultants would be the only certificated investigators and cost effectiveness of the procedure would be in doubt.

This paper undoubtedly adds to the body of knowledge on chronic diarrhoeal disease in childhood. We consider, however, that the inference that toddler's diarrhoea should not be diagnosed without biopsy will strain the credulity of general paediatricians. It remains incontrovertible that suspected coeliac disease must be confirmed histologically but the authors' experience of proving this diagnosis in only one in seven of those suspected clinically demands better prebiopsy criteria. None of the many immunological and tolerance tests described have totally lived up to their original promise but we should look forward to the improvement of screening for coeliac disease both clinically and by such approaches as discriminant analysis of a cohort of tests.[4]

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Archives of Disease in Childhood 1992; 67: 745–750

TYPES OF PSYCHIATRIC TREATMENT

Dealing with the courts and parenting breakdown

Claire Sturge

This is the fifth of a series of articles on treatment of child psychiatric disorders.

The resolution of disputes, problems, and uncertainties through the court system can, as well as safeguarding the interests of the child, actually promote these and be therapeutic. I use here therapeutic in the sense of an agent of positive change, ultimately for the child concerned.

Until now this has been best exemplified in the High Courts. One of the main challenges of the Children Act is whether this tool of positive intervention can be used as constructively and to the full in the lower courts and even transferred out into the community in precourt or no court situations.

Civil court proceedings concerning children and adolescents will almost always be about some form of parenting breakdown.

The purpose of this article is threefold: (1) To explore why child health specialists, particularly child psychiatrists, have come to be involved in the assessment of parenting breakdown[1] and what relevant or essential skills they bring to the decision making process. (2) To demystify court proceedings by clarifying and simplifying. (3) To identify the constructive elements of court processes so that readers can determine how they can have a role in these and extend them to other situations.

The inter-relationship of the courts and child health specialists

Paediatricians and child psychiatrists are increasingly being asked to write reports for court—as expert rather than evidential witnesses—and this is likely to increase further with the Children Act and its emphasis on multidisciplinary assessment.

Courts are clearly mandated to concern themselves with the physical and emotional well being of children. Paediatric assessment, uniquely in medicine, has already moved to considering all aspects of a child's health, including the emotional adjustment and development. While a child psychiatrist may be the one assessing emotional adjustment in detail, the paediatrician has important contributions to make.

What physical abuse did for the paediatrician, sexual abuse has done for the child psychiatrist. The 'discovery' of physical child abuse in the 1950s gradually brought paediatricians into a central role in court proceedings and the 'discovery' of child sexual abuse in the 1980s brought child psychiatrists into the arena. Awareness of sexual abuse and the type of evidence child psychiatrists were giving about its sequelae brought into focus the fact that the most serious and longer lasting effects of *any* abuse are the result of the emotional component of that abuse. We can expect that with this third new awareness, more cases will be brought under the sole category of emotional abuse.

This chain highlighting emotional abuse brings parenting as a whole under scrutiny: emotional abuse becomes equated with gross parenting failure on an emotional level or, put another way, a gross failure to meet a child's psychological needs for his or her healthy emotional development. (Parenting breakdown can, of course, involve other forms of abuse, physical or sexual, but will include an emotional component.)

This recognition has led to examination of how parenting can be analysed, what are its components, and how these can be assessed or measured. There is some agreement on its components but very little on how to measure or assess these systematically.

Parenting assessment

The components are best extracted by considering a child's basic needs (see table 1).

HOW TO ASSESS THESE NEEDS

There are complex schedules for doing this—for example, the social services assessment pack[3]

Table 1 Parenting assessment. the child's basic needs

The needs	*The parenting components*
Security/safety	*Safety* food, warmth, clothing, etc and home, car, road, personal safety *Security* sense of safety necessary for security, stability, and consistency—care givers, care itself, discipline, and boundaries Mutual trust Sense of being listened to and good channels of communication Perception of parents as strong, able to cope, being in control, responsive
Belongingness	Continuity of care givers Clear indentity, for example, names, roots, culture Sense of permanence. Personal/individual space and possessions
Self actualisation/ identity development	Child treated as special and unique Child seen as separate from parent by the parent(s) (distinction of needs). Perceptiveness of child's individuality and particular needs Lack of intrusiveness
Praise/esteem	Meeting of child's need for esteem and praise Expression of warmth and positive feelings, absence of hostility Appropriate positive reinforcement Valuing the child's differentness
New experience/ knowledge	Encouragement of learning, extending new experiences and independence Giving child sense of responsibility for his/her actions and for their impact on others

Modified from Kellmer Pringle and Maslow [1,2]

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and the National Children's Bureau child protection pack.[4] There are assessments based almost entirely on interactional processes—for example those described by Reder,[5] Cox *et al*,[6] Dowdney *et al*,[7] and Bentovim and Gilmour.[8] Questionnaires, checklists, rating scales, for example, a parental bonding instrument,[9] are of limited value in individual cases. Semistructured interviews used in research may have a place.[10]

I take a more pragmatic approach by (i) gathering information (from social services, schools, paediatricians, foster carers, etc) and (ii) making my own assessment of parenting through (a) direct discussions with the parent(s); (b) assessment of the child(ren) to assess their development and particular needs; and (c) observations of interactions between child(ren) and parents. In this way, I attempt to cover all the components of parenting listed above, the details of which vary greatly with age. I pay particular attention to positive remarks about the child, criticism, and indications of warmth or hostility all of which have been consistently shown to be assessable in a fairly reliable way and to relate to quality of parenting.[11] The parent(s) own experience of parenting is important. In situations of breakdown, my experience is that it has invariably been one of insecure or preoccupied type (see Crowell and Feldman[12]).

Having made an initial formulation considering all the components of the parenting needs, I structure (c to target particular areas where problems may lie. If major problems are identified in this way then assessment of the parent's or parents' ability to change must follow.

ASSESSING ABILITY TO CHANGE

Prerequisites

- Acknowledgement of some responsibility for current situation, for example, child being in care.
- Acceptance that there is a need for change and that the parents themselves need to change.
- Acceptance of need for help in this.
- Child should not be used systematically as a scapegoat.

Capacity to change

- History of change/lack of change over time.
- History of cooperativeness and openness with 'helping' professions.
- Ability to reflect during assessment.
- Carryover of content of discussion from one assesment meeting to another indicating change of attitude.
- Tasks can be set to assess this more directly: they can be (i), within session or between session; (ii) directly or indirectly related to problems; and (iii) passive or active.
- Personality/illness/level of intelligence issues are also important factors in ability to change.

For a more comprehensive approach and model see Protchasha and Di Clemente, Bentovim *et al*, and Jones.[13–15] The parent-child game[16] is an interesting new approach to assessing parents' ability to improve on interactional skills.

Predictions about change

These are based on all of above and the input considered necessary to support change.

Exploring alternatives

There needs to be a careful look at alternatives: possibilities for solutions within family/extended family, the resources available for support/therapy, and how the best possible environment for change can be created. Again this is likely to require a collaborative effort with every one in the multiagency network exploring their resources and offering their knowledge of resources available elsewhere.

Under the Children Act, in effect, every request for a full order will be thrown out where it cannot be demonstrated that every avenue has been pursued in looking at means for keeping the family together. Under the Children Act it should be possible to undertake the whole assessment scenario I have described long before, or without any, recourse to court.

The child psychiatrist's contribution

A child psychiatrist has skills in all these areas relating to parenting assessment and the ability to change. Of particular relevance are the following:

- A multiaxial approach to classification, looking at the child in terms of their psychiatric, cognitive, developmental, and biological functioning, and social situation.
- Expertise in family psychiatry resulting from family centred work and the large body of knowledge on family functioning from the different schools of family therapy.
- Knowledge of child development.
- Knowledge about child temperament and its interactional importance.[17]
- Knowledge of adult psychiatry and from this, knowledge about what parenting functions are likely to be impaired in a parent with a psychiatric or personality disorder. The child psychiatrist will also have some knowledge about treatment and prognosis that will be very important in decisions around the child and has easy access to adult psychiatrists to consult over this.
- A 'scientific' approach. Medically trained practitioners do have particular skills to offer in these decision making processes, not simply by virtue of their knowledge base but also as the result of their particular and rigorous training involving the Socratean approach, an emphasis on cause and effect, pros and cons, and a healthy scepticism, particulary in examining evidence.

We are disciplined to think in terms of 'what evidence do I have for making that statement' and on 'what am I basing my opinion.' This approach, which is not so highly developed in other disciplines, together with the knowledge already outlined, will be particularly useful to courts where the issue is centred on whether the harm the child has or may suffer is significant (a central concept in the new Children Act).

Prediction about the child's future is a most difficult and onerous task because far reaching decisions about the child may be based on it. In my opinion, this task falls most appropriately to the child psychiatrist. The child psychiatrist can formulate the problems on a multiaxial basis and base a prognosis on this. The very fact of childhood involves central concepts around the child as a developing being with considerable potential for change, and all the variables of the child's past experience, temperament, present state and future environment impinge on this. Attempts can be made, for example, to answer such questions as to the likely outcome in terms of emotional and behavioural adjustment of a sexually abused child exhibiting traumatised behaviours if she or he remains with the parent, or is in care, and is or is not offered therapy. Child psychiatrists also have a contribution to make in considering transcultural issues in placement decisions where the relative importance of identity development against other development needs must be weighted.

Clearly where there is psychiatric disturbance, the child psychiatrist has an important contribution to make. Particularly difficult cases involve children with an innate problem, for example autism, where a parent's care is in question and the question, under the Children Act, is whether another parent with such a child would be making a better job of it.

Table 2 Parenting breakdown

Problem/concern	*Main focus for assessment in addition to parenting*
Physical abuse	Paediatric assessment risk to health and life. Emotional damage
Sexual abuse	Non-abusing parent's ability to support and protect child Child's emotional state and needs, treatment needs
Failure to thrive physical deprivation	Paediatric assessment
Emotional abuse emotional deprivation	Child's emotional state and needs, treatment needs
Munchausen syndrome by proxy	Paediatric assessment risk to health and life Psychiatric assessment of parent
Parental mental disorder mental illness, personality disorder, substance abuse, mental handicap	Psychiatric/psychology assessment with particular reference to ability to make responsible decisions and progress
Beyond control usually adolescents	Assessment of youngster's needs

Table 2 summarises the common contexts of parenting breakdown and table 3 some of the court mechanisms for dealing with them.

Court decisions

In order for courts to make decisions, the following are necessary.

(1) Identifying the central issue(s) and the questions that need to be answered in order for a decision to be made.

(2) Requiring all parties to justify their actions and criticisms with evidence.

(3) Requiring that the evidence necessary to answer the central questions is produced.

(4) Exploring alternatives, particularly that of no order.

In addition, the courts can be particularly useful in:

- Ensuring very thorough assessment.
- Confronting families with what is at stake—that is, possible loss of the care of a child.
- Making orders compelling compliance where a parent's own motivation is insufficient to result in change. This is, of course, not always successful.[18]
- Clearly defining criteria for measuring change on which future decisions will be based.
- Balancing the power between any individual, for example, a parent and an agency such as social services. Redressing the balance between parties can in itself be therapeutic and is less likely to occur when a case is handled entirely within one agency.

The whole process should be one of clarifying issues and identifying the most objective means of answering questions in relation to them.

The court is attempting to choose the least detrimental option, in the best interests of the child. In practise, it can decide where the child lives, who has day to day and other responsibilities, details of contact with others, and treatment needs. Decisions directly affecting adults are much more limited, particulary in the lower courts.

The party initiating proceedings—for medical practitioners this is usually social services or a parent—initiates this process by deciding what order they are seeking and on what grounds. The initiating party must then seek to produce evidence to support those grounds. The more experienced the initiating solicitor the better the questions will be that are asked in order to elicit information and evidence.

I have been involved in many cases, at the

Table 3 Courts: civil proceedings concerning children and adolescents in magistrates and county courts and High Courts

Issues	*Parties*	*Range of orders/directions*
Parenting breakdown including abuse and being beyond parental control	Social services and others—for example, grandparents	Residence, contact, supervision and care orders, specific directions
School non-attenders	Education authority, parents	Education supervision order
Marital breakdown	Between parents	Residence orders, specific issues, contact (care, control custody, and access are all gone)
Ethnical issues and consent issues	Any	Wardship with its inherent powers *except* full care orders (High Court)
Challenges about statutory services—for example, services to a child 'in need'	Any particularly parents versus education, social services, or the health authority	Judicial review decisions are binding on parties

county court or High Court level, where in effect the dispute is between the parent and a social services department where the parent, for a variety of reasons (often containing a large antiauthoritarian element) has completely fallen out with the social services department and a hostile relationship exists on both sides. The parent's failure to cooperate is then used as further evidence of their lack of responsibility and ability to change. A court can look at this objectively, lean on social services departments, if necessary, to change the social worker or use an independent agency or, if the lack of cooperation is deemed significant in terms of the child's interest, make this explicit to the parent laying down what cooperation the court expects if an order in the parent's favour is to be considered. I have seen very constructive work become possible with the most intransigent parents in this situation (see Familaro *et al*[18]). Of course, it is theoretically possible for this to be achieved by other means, for example the fashionable contracts. These, however, have no legal status and mean social services have 'no teeth' without the backup of a court. Nor do they deal with the power imbalance situation referred to above (see Wolff *et al*[19]).

A vignette

This is a greatly simplified example. A social services department wishes to seek a care order as a result of a mother being found on two occasions drunk and incapable when in charge of her three children under 5 years, one of whom actually went missing. The children are currently on an interim care order, in foster care. The middle child, a boy aged 3, uses no expressive language.

The issue would be: is this mother able to parent responsibly? The questions would be: What are the mother's parenting capacities? To what degree are these affected by drink? What is the prognosis as regards her drinking? How have the children been affected? Is the 3 year old's language problem innate or the result of disturbed emotional development? Is there any way of ensuring these children's safety without removing them? Is there any input which would enable this mother to fulfill her responsibilities?

The social worker involved with the case may have much of this information, but for two reasons additional outside expertise is likely to be required: (1) Social workers do not present their evidence in an 'expert' fashion addressing issues in a systematic manner. This is exacerbated by their own solicitors treating them as inexpert by not requiring reports to answer specific questions but by requiring sworn affidavits, usually of a narrative type, for example on date X I went to the house and found Y. Opinions are not encouraged. (2) The social services department needs to call in outside expertise in areas in which they have little or none. Requirements for the case are shown in table 4.

Table 4 Requirements for a case

Full assessment area to be assessed	*By whom*
Children's health and physical and emotional development	Social services, child health specialist, child psychiatrist
The mother's own history	Social services and child health professionals
Stresses on the mother	
The mother's parenting abilities	Social services, child psychiatrist, clinical child psychologist, or combination of these
Mother's ability to change	
Mother's mental state, alcohol problem and its prognosis	Adult psychiatry

As can be seen, a collaborative effort is required and there will be important inputs from the health visitor, general practitioner, nursery if applicable, and others who know the mother and children.

The concept of multidisciplinary assessment in addressing the needs of children is central to the new Children Act. The social services department usually initiates and coordinates such multidisciplinary assessments, including child assessment orders (in which the courts can control the nature of the assessment). While child psychiatrists may, for the present, be the group able to contribute most comprehensively to parenting assessment, their numbers are too few to be involved in all cases. Others, particularly clinical psychologists specialising in children, have a great deal to offer.

I do believe that child psychiatrists' skills are essential in certain complex situations:

- Where the child has a marked psychiatric disorder.
- Where a child's or adolescent's allegations are subject to doubt because of contradictions, inconsistencies, clearly fanciful parts, or a history of lying or fantasising. (The whole area of how to approach the validation of allegations is a subject in itself.)
- Where the parent has a marked psychiatric disorder.
- Where there is a need to interpret the meaning of a child's behaviour, for example, emotional reactions to contact with a parent or non-verbal behaviours such as play or acting out.
- Where there is a need to determine prognosis about a child's disorder.
- Where there is a Munchausen by proxy type situation in which for example a parent's overwhelming belief that a child has been sexually abused, in the absence of any evidence, becomes in itself, abusive.

Tips

Questions to be considered when you become involved in court proceedings: Who is instructing you? If this is your own local authority, the assessment is under your NHS contract, the writing of a report for court or attendance at court is section 2 work. If it is the local authority, check whether a *Guardian Ad Litem* has been appointed. If so, insist he or she is consulted about social services instructing you. If the guardian approves your doing the assessment this will avoid duplication—important for the child but also in order to conserve our own overstretched resources. If it is the guardian or a private solicitor all the work will be section 2 work and will be usually paid out of legal aid monies which are very restricting. It can take up a lot of time negotiating what can be done for a specified sum. Ethically this can be difficult—is half an assessment better than none?

Whoever is instructing you the most important thing, and that which will determine the quality of the whole process, is the questions you are asked to answer. Make sure these questions are entirely open—that is not 'should this mother ever see her children again?' but 'what is your opinion on future contact between mother and children?'. It is well worth the investment of time in getting questions clarified and if I get very biased questions, particularly from a private solicitor, this may determine me against taking the case.

Always get prior agreement to your report going to all parties. Your report is by definition unbiased but can be suppressed by the instructing solicitor. Occasionally I even go as far as sending a copy to the clerk of the court.

If the request comes from your local authority, consider whether you will be able to act in a sufficiently independent way. It can be very difficult to implicitly criticise one's local department or make costly recommendations and then continue working with the department day to day.

Reports usually need to be long where difficult decisions are involved so as to include all the evidence and alternative arguments. The summary and recommendations should be short. The recommendations, though most attention is paid to them, are the least important as our job is to give the court all the necessary information to inform its decisions. My reports vary from five to 50 pages (the latter if there are several children and a large variety of possible outcomes).

It is worth forging links with the local courts, for example expressing a wish to meet the magistrates and the borough solicitors. I am usually not called in the lower courts and if I am, the borough solicitors and the courts do everything in their power to make this as convenient as possible.

Child Psychiatry and the Law is a most useful reference book when involved in court work.[20]

General comment

I hope this article has made clear that by the very process of clarification and careful, objective assesment together with their innate authority, courts can have a very positive effect in furthering children's interests. For this reason, while welcoming the Children Act as the most exciting step taken in children's interests in my working life time, I am concerned over the inevitable impact of the act in relation to court proceedings.

(1) Wardship has virtually disappeared and in particular I believe this deprives parents (and therefore the child) of the highest level of judicial consideration where a parent may be overpowered in a situation of conflict with a statutory body.

(2) There will be a downwards movement in terms of the level of court. All cases will start in the Family Proceedings Courts and most will stay there. We have yet to see how easy it is to get the more complex cases moved up to higher courts. My knowledge of magistrates and their training, and the solicitors and barristers involved in these lower proceedings makes me very concerned that children will lose out because of lesser expertise. Complexity will be gauged by the intensity of the 'war', that is the number of affadavits, rather than on the actual wisdom required to decide a multi-issue situation for a child.

The important thing is to be aware of, and to address these issues. Any party can apply to the registrar for a transfer of court and the health authority may in future see cause to make itself a party more frequently.

(3) My third concern relevant to this article is the concept of theoretically ever extending parental responsibility for children so that they can have multiple 'parents'. While useful for adults in underlining concepts of responsibilities rather than rights, I believe it will be confusing for children and their need for clarity and security.

(4) My fourth major concern is that without the high court there is no court review procedure. Once a child is in care, there is no process that allows a court to review how social services is progressing the case, for example no curb on delays, say, in finding a long term placement. Social services may welcome this, I do not. This also denies magistrates the opportunity to learn from the experience of seeing how court decisions turn out.

(5) My fifth concern relates to problems that are likely to result from over stretched resources within all the agencies. This will affect: (a) assessment in general: there is likely to be a conscious or unconscious resistance to take on in depth assessment work. I am continually struck by how even the consideration of court proceedings, and certainly actual court proceedings, can transform a case and get movement and outcomes not originally considered possible —as a result of the processes I have described of clarifying issues and trying to answer questions around these issues. In addition the particular skills of the legal profession in the process of clarification and objective assessment will not be available where legal proceedings are not being considered. (b) The provision of alternatives. With the lack of financial resource in social services and treatment facilities within the health authority and social services, some families are likely to be treated unfairly. If an intensive treatment resource is not available care may be the only course where there are major parenting problems. One is often faced with the dilemma of whether to recommend an approach to enable change when one knows the resource is not available through the local health authority or social services and may need to be paid for in the independent sector. This is a particular problem when working with one's own local authority.

I look forward positively to a future in which we can continue to develop ways of working with the courts that make use of the very constructive processes that I have outlined and in which we all learn to take those processes of assessment and intervention, which can also be productive outside of the legal framework, into our interagency work.

I find this type of work often to be doubly satisfying: it is intellectually the most challenging I undertake and in terms of altering children's lives for the better often the most effective input I can have.

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Recommended reading

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Archives of Disease in Childhood 1992; 67: 751–756

CHALLENGES

Child health and paediatric care in Spain: where are we going?

Angel Ballabriga

This is the fourth paper in a series showing the problems facing the medical services for children in different countries.

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The National Health Service

The National Health Service (NHS), providing free medical care, was initiated in 1945 to cover part of the Spanish population, and was then progressively expanded to the entire population. In 1950 the NHS incorporated paediatricians to give paediatric care to children from 0 to 8 years of age. In the 1960s great structural improvements took place, including the inauguration of five large well equipped children's hospitals. During the next 11 years the level of hospital care for children was dramatically improved, after which important changes in the administrative structure were introduced, which in our opinion have not favoured development of the paediatric service.

Since 1977, there have been important political discussions concerning the 'model of medical care' to be applied. Spain has become a so called state of autonomies, with 16 geographical areas with different degrees of independence from the political and administrative points of view, including public health care. At present, there is a mixed medical model, in which all the population is affiliated to the NHS by obligation, coexisting with the practice of private liberal medicine and medical care obtained through voluntary membership at their own cost to insurance companies. In some large geographical areas there is a total degree of administrative autonomy concerning medical care organisation, in other areas there is partial autonomy, and in others medical care depends completely on the central government Health Ministry. This causes differences in priorities and for these different reasons, sometimes even due to political prestige, some public health programmes receive more attention than others. In our opinion, this could lead in the short term to a loss of homogeneity in the distribution of medical care.

Over the last few years, criticism of the NHS has strongly increased and even the media comment on the chaotic situation of this service. Others, still more critical, use public health as a political arm to collect votes or for internal manoeuvres in political parties. Faced with this situation the administration talks about the need for decentralisation and autonomy for hospitals and health centres but this question remains for the moment as pure speculation. The Blendon survey,[1] carried out recently in Spain to discover the degree of satisfaction felt by the users of the NHS, shows that 25% thought that the system should be completely changed and another 49% considered that fundamental changes should be introduced. It is very significant that even with these very negative aspects, 71% of NHS users demonstrated their approval of the quality of medical care received. Their criticism was of the organisation, efficiency, bureaucracy, and financing of the system. Now there is a confrontation of two opposite views: on one hand, the trend towards a scientific approach to the problems, supported by the majority of physicians and, on the other, the orientation to a purely economical management as first priority. This latter is represented by a new elite of economists and some young physicians acting as state bureaucrats, politically dependent on the system. Putting government economists in charge of the hospitals added a humiliating loss of control for the physicians.[2]

It is evident that a good financial balance should be obtained and that public health medical expenses must be controlled. However, in our opinion the solution does not lie in rigid economies but rather in the avoidance of squandering money for political gain. On the other hand, if physicians had better opportunities for continuous medical education and greater satisfaction in their work, expenses would be reduced. The fact is that although the public health budgets have multiplied threefold in the last nine years, general discontent still remains. Public health expenses as a percentage of the gross national product is 4·5 in Spain, compared with 5·3 in the UK, 6·3 in Germany, 6·7 in France, and 8·3 in Sweden.[3] Recently, as a consequence of the continuous polemics about public health the Spanish parliament requested a report from a committee concerning the matter and the so called Abril report was born.[4] From this report, the failure of the NHS management is clear. The expenses of medication are 20% of the total. For some this report is very pragmatic and full of common sense and for others it is cold and niggardly. Waiting lists are very long although Spain, when compared with other countries, has more physicians for the total population and an enormous number of unemployed young physicians. Some autonomous communities, such as Catalonia, try to liberate themselves from this situation with more good will than success; despite a great display of propaganda, consumers ask for a more flexible and less bureaucratic public health system, and the public health workers are dissatisfied and unmotivated.

Development of paediatrics

In the development of Spanish paediatrics during the last five decades, three stages must be differentiated. The first was a phase of restrictions from 1945 to 1960, after the Spanish Civil War and the second world war, with a precarious economy and international isolation and with high infant mortality and children's diseases typical of developing countries. Paediatric public health was orientated towards programmes of vaccinations, nutrition, and well baby clinics.

The second stage was a phase of expansion from 1960 to 1975. The international isolation progressively disappeared, the economy improved, international scientific contacts became easier, and large paediatric hospitals were inaugurated. At the same time, paediatric specialties began to be developed in these hospitals and educational programmes were started at national level for residents in paediatrics; the number of faculties of medicine were increased and better facilities for research could be obtained This was a time of great prosperity for paediatrics. Curiously, we disposed of modern equipment facilities which had been suitable to treat diseases typical of developing countries. The medical panorama had completely changed, the reduction of infant and perinatal mortality was dramatic, and the diseases common to undeveloped countries gave way to those of developed countries. There was an enormous improvement in the quality of medical care in hospitals, but less quality in primary care.

The third stage, since 1975, is a phase of stagnation, and at times regression. Our country has passed in the course of a few decades from a semideveloped to a highly developed industrialised society, the birth rate is declining dramatically and the development of family planning is enormous. Many years ago, paediatrics officially included only children up to the age of 8 years, but now the age limit has been increased to 15 years. In the memorandum presented by the Board of the Spanish Paediatric Association to the Minister of Public Health in 1989, our association expressed concern about the scarce attention that the administration dedicates to the child.[5] The investments are made too late, are uncoordinated, and are unproductive. The fact that infant mortality has decreased to satisfactory figures does not justify decreasing attention to the child. Generally, our complaints fall on deaf ears and the administration maintains an arrogant attitude and our politicians badly tolerate criticism.

The Educational programme for residents in paediatrics (MIR programme) in recent years has resulted in a considerable number of physicians obtaining a high degree of specialisation. They have occupied new positions in health centres for primary care, resulting in a great improvement in the quality of assistance. This new paediatrics presumes a reduced number of admissions of children to hospital but who have more sophisticated problems. The administration has reacted by facing this new situation with a remarkable lack of imagination. A paediatric hospital completely ready for use was not even opened and many floors of paediatric hospitals are being converted for adult care while the opportunity is being lost of giving more attention and development to the problems of adolescence that must be included in paediatrics, together with the creation of new programmes for rehabilitation, attention to emotional disturbance, and teenage pregnancies.

Vital statistics in Spain

	1965	*1970*	*1975*	*1980*	*1985*	*1986*	*1987*	*1988*	*1989*	*1990*
Infant mortality	37·3	25·4	18·9	12·3	8·9	9·2	9·0	8·5	7·8	
Perinatal mortality		25·4	21·1	14·5	11·0	10·7				
Neonatal mortality			12·6	8·5	5·9	6·2				
Birth rate	21·1		18·8	15·2	11·8	11·2	10·8	10·7	10·4	10·26
Total population (millions)	31.9		35·4		37·7					38·9

All data after 1986 are provisional.

Vital statistics

The infant mortality rate, perinatal mortality, neonatal mortality, birth rate per 1000 population, and total estimated population over the last decades and in recent years are shown in the table.[6–9] The fertility rate in 1960 was 2·9 and in 1987 was 1·7. The total number of paediatricians registered in Spain in 1990 was 8421.

Neonatology aspects

Since 1960 there has been a notable decrease of perinatal and neonatal mortality, but the distribution for geographical areas is not uniform throughout Spain.[10] Perinatal mortality in 1984 shows a maximum of 15·09 in the Rioja area and a minimum of 6·14 in Catalonia. Early neonatal mortality represents 51·6% of the total infant mortality. Social and clinical modality variables associated with perinatal mortality in Spain over a period of five years have been studied[11] and an analysis made of the correlation and linear regression between perinatal mortality and socioeconomical variables such as family income, percentage of active population of the primary sector, percentage of women of fertile age with elementary or high school education, number of beds for obstetrics and neonatology, and the number of active obstetricians and paediatricians for 1000 live births. This study showed that the maximum correlation corresponded to the disposable family income, while the number of maternal and neonatal beds per 1000 live births did not show a significant correlation. In Barcelona City, perinatal mortality in the different districts shows a rate ranging between 20·7 and 8·64,[12] the difference depending on the socioeconomic condition of the families that live in certain areas, all of whom have the same free access to the medical service. More valid information is necessary concerning incidence and timing of perinatal death, to establish appropriate strategies. For this, the establishment of rapid and efficient systems for data collection is necessary. The present system is bad and delayed, and there are no banks of public health data that are sufficiently up to date for consultation. The future of neonatology in our country must include greater effort to improve the survival of very low birthweight infants.[13] This particular group remains one with high rates of death and disability. Perhaps it is more important to obtain not only better care but better babies in women of very low income. The priorities for neonatology must include not only more money for more sophisticated units but more money for prevention and intervention programmes for families with a very low income. Likewise, an increase in health education is necessary so that pregnant women attend antenatal clinics more often.

Another important problem is neonatal transportation. The problem is not solved only with good organisation of 'newborn transfers' but with a preventive 'maternal-fetal transfer'. The Neonatology Section of the Spanish Paediatric Association has sounded a note of alarm concerning the inadequate conditions during transport of newborn infants to referral centres. Education of the public and policy makers about the importance of reducing the numbers of low birthweight babies should be emphasised. The magnitude of preventable death occurring during the neonatal period must be evaluated. This is not a call for reducing budgets for technology or stopping medical progress, but rather a call for spending more money for identifying problems where a solution requires other methods.

Low birthweight infants represent between 5% and 7% of newborns in our country. A survey including 5345 newborn infants in 16 different centres in Spain showed that the proportion of infants of low birth weight of less than 2500 g was 4·87% in 1982 and 7·17% in 1989[14]; of these 0·8% in 1982 corresponded to infants of less than 1500 g and in 1989 it was 1·42%. These data show a negative trend with a progressive increase in the rate of low birth weight. If this tendency is maintained, at the end of this century we will have rates typical of a developing country. Of this group of low birthweight infants, 7·2% of the mothers were under 20 years of age, 31% were smokers and, once aware of the pregnancy, only 14% stopped smoking. Priority should be given to antenatal clinics in the integral planning of mother and child care.

Nutrition

Data from 1965 show that the incidence of breast feeding was around 89%. This decreased progressively to approximately 41·5% in 1983 before rising again to 82% in the next six years.[15] The figures vary in different areas in Spain and also according to the different sociocultural levels. The average duration of breast feeding also differs, for example 2·7 and 3·3 months, and only 13% maintain lactation to the sixth month; 8·38% of the mother were smokers. Early ending of breast feeding occurred more frequently in young mothers from the lower cultural and socioeconomic groups. Study of pesticides in human milk shows high concentrations but not values regarded as toxic.[16] The reason most often cited for using breast milk substitutes was a decrease in the milk flow; mother's work played a part in only 6·4% of cases.[17] Before 12 months of age 44·5% of infants received fresh cows' milk and in 21% of cases complementary feeding with solids was given before 3 months of age.

The general state of nutrition of the child population in Spain at the present time can be considered as very good. Cases of malnutrition commonly existed up to the 1950s but our society is now becoming one suffering from overnutrition. The rate of obesity in our child population has been established as 5·8% in rural areas, and 4·8% in urban areas, and 4% in metropolitan areas.[18] We emphasise the existence of bad feeding habits in adolescents caused by the introduction of new life styles and high consumption of hamburgers, pizza, take away foods, and in certain groups junk diets. In at least 10 different surveys in different parts of Spain hypercholesterolaemia has been found in schoolchildren and adolescents, which was related to diets with high intake of saturated fats and cholesterol.[19] In Spain an important trend of increasing height of the population has occurred throughout this century, this being particularly noticeable during the last 20 years.[20]

Concerning dental caries, some local community programmes for buccal and dental health have been integrated into school schedules, and the distribution of oral fluoride solutions in health centres has been started for children between 6 months to 14 years of age. However, various studies still show dental caries in 59·6% of schoolchildren, and health education must be improved in this respect. The NHS is very deficient in providing buccal and dental care for children.

Metabolic screening and congenital malformations

The programme for prevention of congenital metabolic diseases includes 18 centres orientated to the detection of phenylketonuria and hypothyroidism in newborn infants. The incidence found is 1/26 526 for phenylketonuria, 1/17 684 for hyperphenylalinaemia, and 1/2500 for hypothyroidism.[21] Some of these centres also work with a programme of detection of 21-hydroxylase deficiency, which has an incidence of 1/12 379 for homozygotes. The percentage of false positives was 1·7%.

As regards cystic fibrosis the Δ F508 mutation accounts for only a small part of the total range of cystic fibrosis defects in Spain. In southern Europe the Δ F508 mutation is 52·9% compared with 75·6% in northern Europe, which means that between 25% and 50% of couples will still need to undergo tests with the marker closely linked to the cystic fibrosis gene, as they do not have the Δ F508 mutation.[22]

The Spanish collaborative study performed between 1976 and 1985 on 551 902 newborn infants showed 11 099 congenital defects.[23] For every 1000 live births the proportion with congenital dislocation of the hip was 4·1, for foot deformities 2·18, for hypospadias 1·84, for Down's syndrome 1·5, and for spina bifida 0·42. Since 1984 the alcoholic fetal encephalopathy syndrome has also been included in the list, with an incidence of 0·17 for every 100 000.

Health centres

Recently, many of the outpatient paediatric consultations have been transferred to health centres in which there is a coordinated team giving primary care with a high level of coordination between hospitals and health centres. The idea is to work with less bureaucracy and more flexibility, giving primary paediatric care together with preventive aspects and rehabilitation in combination with social services. The aim of the health centre is also to avoid the physician's feeling of frustration faced with routine and to study environmental conditions with the intention of introducing intervention programmes. In this way integral paediatrics is established in a limited geographical area. These centres can also be useful for the training of resident physicians working in large hospitals.

Infectious diseases and vaccination

The pattern of infectious diseases in Spain has changed substantially during the last three decades. Prevalent diseases before the 1960s such as diphtheria and poliomyelitis have disappeared thanks to vaccination programmes. Measles is strongly declining and also tuberculosis. A cross sectional survey in the city of Barcelona on immunisation coverage of 2 year old children in 1988 demonstrated that vaccination coverage was 93·1% for measles, 92·0% for mumps, and 91·2% for rubella. Up to 91·2% of children have received four doses of polio vaccine, and 91·6% have received four doses of the combined diphtheria, tetanus, and pertussis vaccine.[24] The degree of the mother's education is closely correlated with the level of vaccine coverage. The general target is to achieve 93% of coverage for all vaccines in children between 4 and 6 years old for 1995, and reach 97% for the year 2000.[25]

Meningococcal infection is endemic but the rates are dropping, in 1983–5 the rate was 8·85/100 000 inhabitants, and in 1990 it was 3·04. Of these, 78% of cases correspond to patients of less than 15 years of age. Meningococcal typing shows that 81–85% correspond to group B and 14·1% to group C. Penicillin resistant strains have been isolated in 13 provinces and 0·3% of the strains studied was resistant to rifampicin.[26]

In neonatal meningitis there is a predominance of streptococcus B, *Escherichia coli*, and listeria. Gastrointestinal infections have changed with a decrease of *E coli* infections and an increase of infections by salmonella, campylobacter, rotavirus, yersinia, and cryptosporidium. Visceral leishmaniasis has decreased and now in certain areas has a rate of 2·12 cases/100 000 inhabitants, the high risk group being children between 0 and 4 years of age. This infection is related with the existence of canine leishmaniasis with rates of 1·6 to 15% in dogs according to different areas. Boutonneuse fever caused by *Rickettsia conori* a prevalent disease in Mediterranean areas, is observed in our children but not often.[27]

Two very important problems concerning infectious disease in children are hepatitis and AIDS. A study of hepatitis markers in the school population in Catalonia shows that the incidence for hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody in children between 6 and 14 years was 0·4 and 0·8 respectively and the incidence increases between 15 and 24 years to rates of 1·7 and 9·3 respectively, demonstrating that infection is mainly acquired during adolescence. In this area, a selective programme of vaccination directed to adolescents and high risk groups, including newborns of HBsAg positive mothers, has been developed.[25] Concerning AIDS, a survey comprising 83 paediatric centres carried out between 1981 and 1989 reported 1938 cases of HIV positive infants born to HIV positive mothers.[28] Of these cases, 33·3% were from Madrid and 24·2% from Catalonia. This study has demonstrated that at this moment the number of HIV positive infants born to positive mothers is higher in Spain than the total cases from six other European countries together. Infants contaminated by transfusions and haemophilic children have been excluded from these statistics. The rate of infection of these 1938 cases at 18 months of age was 25·6% and in this group 55% already had clinical symptoms. Of the mothers, 93% were parenteral drug abusers and 33% of these babies were of low birth weight. We see an incidence of one HIV positive newborn/1000 deliveries, but our survey included only public hospitals; as 35% of deliveries take place in private clinics, the figures of the survey represent only the tip of the iceberg. We need the development of adequate multidisciplinary units to follow up these children. On the other hand, HIV positive neonates are one of the most discriminated and unprotected groups of our society because they are not being openly supported by the respective HIV pressure groups.[29] For this reason, it is necessary that health authorities, the mass media, and the general public combat this discrimination and compensate for the absence of a pressure group for children.

Accidents in childhood

Accidents represent 20% of emergencies in children's hospitals in our country and 25% of admissions to paediatric intensive care units. If neonatology is excluded, accidents correspond to 13% of all admissions in our paediatric hospitals. Blows and falls constituted 76·1% of accidents in a survey of 5021 cases. The main incidence is between 0 and 4 years of age and the accidents are usually at home, particularly in the kitchen. Traffic accidents, however, are the main cause of accidental death in childhood, the greatest incidence being in the groups of 5–9 and 10–14 years.[30] Intoxication and burns are more frequent between 1 and 4 years.

Transplantation in children

The law that established regulations for transplantation in our country was passed in 1979. Terminal renal failure in children has a rate of 5·2 per million children a year. For the development of the kidney transplantation programme, Spain covers five different geographical areas, each area including 5–8 million inhabitants, and a further area covering the Canary Islands. Children's kidney transplantations are performed in the surgical departments of paediatric hospitals. Up to 1989 there have been 77 paediatric liver transplantations performed in three centres with survival rates similar to other European series. There are also special units for bone marrow transplantation in children.

Teenage problems

At present, adolescents are not officially integrated into paediatric hospitals but in recent years adolescence has progressively become part of the paediatric education programme and in some hospitals we have started its incorporation in paediatrics. The increasing presence of problems such as teenage pregnancy, drug addiction, nutritional problems related to life styles, and sexually transmissable diseases in early adolescence make it necessary. Alcohol consumption is a very important problem in our country and different studies show that between 56·6% and 71·6% of students drink alcohol.[31] In another study, 89% of teenagers were beer drinkers and 92·1% said they had no problems about buying alcohol,[30] although the law does not allow it at this age. The incidence of alcohol consumption was higher in groups of low socioeconomic status, particularly in children of unskilled workers. There is a close statistical correlation between smoking and alcohol consumption.[32] Regarding the habit of smoking, a study in teenagers demonstrated that at 10 years of age it was of 9% and at 18 years it had risen to 63%.[33] In our country, from 1957–80 sales of cigarettes increased by 150% while in the same period the population had only increased by 22%. The study of 25 130 children between 12 and 18 years in Cadiz showed that 25% smoked in the street and 21% smoked in school, although it is prohibited there.[34] Although the prevention campaigns have intensified, we should not forget that both tobacco and alcohol are good sources of income for the government. Consumption of psychoactive drugs is a key problem in public health in Spain. The trafficking of drugs in Spain is punished by law but personal consumption is not. At present there are even public demonstrations against drugs. In young mothers drug abuse has played the main part as the mechanism of AIDS transmission. The average age for starting heroin is 18 years but earlier cases, around the age of 10, are not uncommon and the age for starting inhaled solvents is 8 years.[35] Cannabis smoked with tobacco is the most frequent addiction. Cocaine consumption occurred in 3% of youngsters between 16 and 20 years in 1989. The main problem is the subsequent behaviour that is caused by drug addiction.

Training in paediatrics

The national programme to obtain the certificate of specialist in paediatrics demands training as a resident in an accredited paediatric department for four years, during which period there is remuneration. This programme was started in 1966. The number of candidates trying to obtain a position on this programme is usually from six to 10 for each available place. In 1991 there were 3701 positions for all specialties inside this programme, of which 25% were dedicated to family medicine and 215 (5·8%) were devoted to paediatrics. The selection takes place at a national level, through a multiple choice test. In our opinion this method is full of problems and does not allow for an adequate selection of candidates as there is no information about the skills of communication and there is no personal interview of the candidate.[36] On the other hand, we believe that the current restriction in specialisation makes no sense; if this has to be made, it should be at the beginning of studies not at the end. Even with the problems of the programme, it has been more useful than previous schemes and has provided well trained paediatricians. At present there is no official recognition of subspecialties in paediatrics except for paediatric surgery, for which the training is five years. Of course, during the residents' programmes there is rotation that takes in the different subspecialities and in many cases the final two years allow greater attention to a certain subspecialty.

In a prospective study concerning medical practice published in 1980 a group of experts stated in relation to medical research that 'the research is very interesting, a high number of professionals are interested, it is badly paid work and practically non-existent'.[37] Preliminary drafts of the report indicated that Spanish medicine, of course including paediatrics, would in 10 years have a structure with the same style as that of the more advanced Western countries. Unfortunately, I am of the opinion that this statement has not been confirmed, although certain facilities are now possible with grants obtained through official research programmes.

Where are we going?

In spite of the strong criticism we make about the system, the progress in the development of paediatrics in our country over the last 25 years has been enormous and the contribution of our paediatricians has been more than generous and efficient. It has not, however, been possible to achieve all the goals initially proposed and it would be desirable that our administration, both central and autonomous, be less arrogant, less dogmatic, less bureaucratic, more flexible, more ready to accept criticism, and more cooperative with professionals who still maintain a pure scientific spirit. In this way it would be possible to establish and discuss a balance between finance, salaries, expenses, management, scientific perspectives and priorities and so allow for good progress in a not too far distant future. Priorities are always a very delicate subject. It is evident that high technology must be developed, but one should not be dazzled by it, and at the same time basic paediatric services should be homogeneous throughout the country.

Government expenditure on public health has notably increased over recent years, but this is still not enough for good paediatrics and to include prevention programmes. More financial support is needed and for this perhaps other sources of finance are necessary. The increase of public expenditure in Spain is enormous and important allocations of the government's budget go to trade unions, political parties, and bureaucracy. Perhaps it is there where restrictions should be made, as tax capacity has already been saturated.

In spite of all of this, we still feel happy! Because for the moment when we are sick we can go to our NHS doctor. Perhaps in a near future we will be obliged to go first to our NHS economist.

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Archives of Disease in Childhood 1992; 67: 757–759

STATISTICS FROM THE INSIDE

6. Data structures (continued)

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No reprints available

Two level structures

Situations arise when experimental units (subunits) can be combined to form larger units (main units) which can be treated as a whole. For example, responses to several concentrations of an allergen could be measured at sites on the forearms of individual subjects. It might be required to investigate the effect on these responses of two alternative systemic drug treatments. The forearm sites (which receive the different concentrations of allergen) are then the subunits, while the subjects (who receive the drug treatments) are the main units. A design of this kind is usually referred to as a *split unit* layout. When the results are analysed there will be two different error variances, one relating to comparisons between subunits and the other to comparisons between main units. The first of these will normally be the smaller of the two, perhaps by a substantial margin.

The commonest form of split unit experiment in clinical work is the familiar 2×2 crossover trial in which two treatments A and B are administered successively to each subject, half the subjects receiving the sequence AB and the other half the sequence BA across the two treatment periods. The main units are the subjects, the subunits are the treatment occasions. The contrasts between treatments and between periods are subunit (within-subject) comparisons and as such are likely to be fairly precise. However, for these comparisons to be valid it is important that the two treatment sequences do not give different results. The contrast between sequences is a main unit (between-subject) comparison and so is likely to be noticeably less precise. The test for the presence of a difference between sequences may thus lack power (a substantial true difference may yield a non-significant result with high probability), so that an invalid experiment is liable to go undetected. A common source of differences between the treatment sequences is *carry over*, the residual effect of the treatment applied first lasting over into the second period. The two level data structure means that carry over may be present to a substantial degree and yet remain undetected. Crossover trials are only suitable for comparing treatments whose effects are known to be transient, and the experimental periods should be so arranged that the possibility of carry over is minimised.

Two level data arise in a number of circumstances, both experimental and observational. One of these is the study of laboratory performance, when it is usually necessary to distinguish between the within-batch and between-batch precision of a particular technique. Another is the situation in which some physiological quantity varies both between and within subjects. In this context it is often necessary to distinguish not only between within-subject and between-subject variation[*] in a single quantity, but also between the within-subject and between-subject regressions relating one quantity to another. Both these common situations are often misunderstood and I hope to return to them later in this series. On a larger scale, multicentre clinical trials provide two level data, with the centres as main units and the subjects as subunits. Such trials are almost always analysed with no account taken of the possibility that the average effect of treatment may differ from one centre to another. Recent statistical developments with associated software are making it possible to undertake more thorough analyses of data like these.

Repeated measures

A superficially similar data structure of very frequent occurrence is the repeated measures design in which an outcome measure is made repeatedly on several occasions on each subject—an example is a glucose tolerance test in which blood glucose is measured at regular intervals after glucose intake. The distinctive feature of this structure is that the sequence of observations cannot be randomised. In a split unit trial, randomising the allocation of the treatments to the subunits within each main unit ensures the validity of the standard analysis; with repeated measures, error discrepancies between occasions far apart in time are liable to be larger than those between neighbouring occasions and the standard split unit analysis does not allow for this. Many textbooks and computer programs do not recognise this distinction and present a split unit analysis under a repeated measures heading. Use of these 'standard repeated measures' analyses is liable to produce erroneous results.

One approach to repeated measures data consists in analysing each of the measurement occasions separately. This cannot be said to be incorrect, but it is liable to fail to extract much of the information from the data and can be quite misleading. The different occasions will not be statistically independent so that it will be difficult to combine the evidence that they individually provide. Perhaps more importantly, it will frequently be the case that the curve joining the occasion means will not agree with the corresponding curve for any of the individual subjects—this will be so when the individual curves differ mainly by way of expansion or contraction of the time scale (so called tempo effects). This last point is illustrated by fig 1, which shows concentration/time curves for drug concentrations in five patients. The heavy line is that joining the means for each time of the five curves. This last line answers such questions as 'What is the mean concentration at 12 minutes?', but it is of a different shape from the individual curves and it fails to answer more interesting questions such as 'What is the mean of the maximum concentrations?'.

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[*] The terms intrasubject and intersubject variation are often used, but the distinction is important enough to be worth a difference of more than two letters.

A better approach is to try to obtain a small number of derived quantities for each subject which adequately summarise the time course of the observations. If for example the readings increased steadily with time, the slopes for the individual subjects can be calculated. If the response rises to a peak and then falls back as in fig 1, the height of the peak or the area under the curve can be used, perhaps together with the time at which the peak occurs. Each summary measure represents a single variate with a reading for each subject and these readings can be analysed in the usual way. A fuller treatment of this important topic is given by J N S Matthews, D Altman, M J Campbell and P Royston. Analysis of serial measurements in medical research, *BMJ* 1990;**300**:230–5. This paper also addresses the difficult issue of how data of this kind should be presented. The usual technique of displaying simply the occasion means with error bars of some kind, the outcome of separate analyses for each occasion, has been seen above to be inadequate if not actively misleading.

When repeated measures data occur in an experimental context, a special consideration often arises. The subjects or other experimental units will be (or at least should be) allocated to the different treatment groups by a process of randomisation. This means that we know for a fact that at time zero the treatment groups constitute random samples from a single population. This in turn implies that the population means of the different treatments at time zero are all equal. A statistical adjustment,† compensating for initial differences in the sample means, can sometimes lead to substantial increases in precision and hence to more conclusive results.

Another aspect of the same topic, the fact that the true mean time curves of the different treatments all start at the same point, is the so called race track effect. Suppose for simplicity that the time course of the readings follows a straight line (as with short term growth phenomena). Then the mean treatment differences, which are initially zero, will increase steadily with time (fig 2) and will be evident both in the average heights of each line above the axis and also in the slopes of the lines. In race track terms, the horses that run faster are also the ones that go farther. If the raw data are subjected to a 'standard repeated measures' analysis of variance, the differences will show up in both parts of the analysis, as a main effect of treatment and an interaction between treatment and time, a thoroughly confusing description of what is in fact a straightforward state of affairs.

Treatment structures—factorial trails

Returning to our example involving the effects of different drugs on the responses to an allergen, in the simplest case there will be two allergen concentrations and two drug treatments. The trial as a whole then includes four treatments:

Drug A—low concentration
—high concentration
Drug B—low concentration
—high concentration

and these treatments now have a structure. Specifically, the four treatments consist of all the combinations generated by two *factors* (here, drug and allergen concentration) each at two *levels* (A and B, low and high respectively). Such a trial is called a 2×2 *factorial* arrangement.

The factorial treatment structure needs to be taken into account in the analysis of the results of the trial. Comparisons between the four treatment means give rise to three degrees of freedom

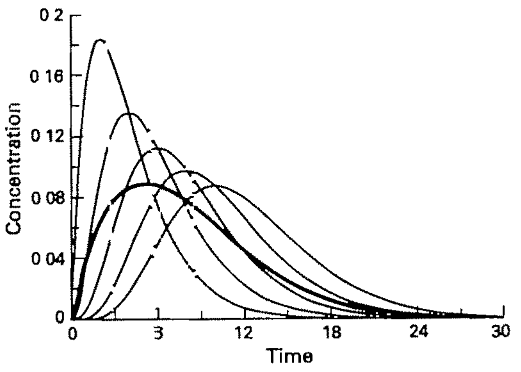

Figure 1 Concentration v time for drug concentrations in five patients The heavy line shows the mean concentration at each time

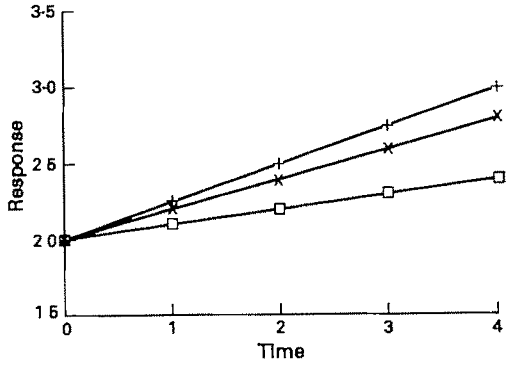

Figure 2 Response v time for three treatments in an experiment with repeated measures

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†The appropriate technique is known as the *analysis of covariance*—see a forthcoming note on regression in this series

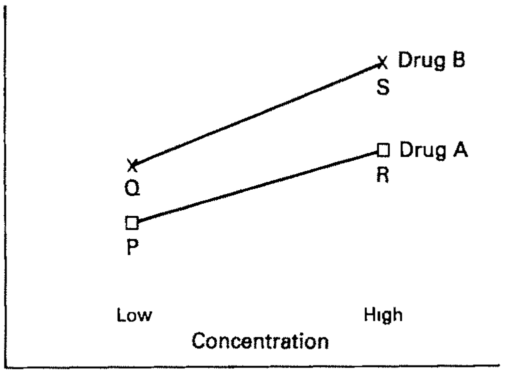

Figure 3 Treatment means from a 2×2 factorial trial. The difference between the drugs is greater at the high concentration (RS) than at the low concentration (PQ)

and these can be split into three individual contrasts:

(1) The difference between drug A and drug B, averaged over the two concentrations;

(2) The difference between the high and low concentrations, averaged over the two drugs;

(3) The *interaction* contrast, the extent to which the difference between drugs is influenced by concentration.

The first two of these are known as the *main effects* of the two factors.

The concept of interaction is an important one. It can be illustrated in fig 3. The treatment differences between the drugs at the two concentrations are given by PQ and RS, and interaction is present when these are unequal. If PQ is equal to RS, so that the two lines in the diagram are parallel, the two factors do not interact and they are said to be *additive* in their effects. It should be noted that when the two factors do interact, the main effects are unlikely to be of any interest; one cannot talk of *the* difference between the drugs when this difference depends upon which concentration is being used. This means that, when the results of a factorial trial are being considered, consideration of the possibility of interaction is logically the first step to take.

Factorial trials are by no means confined to the two level data structure, and the possibility of incorporating an extra factor in a contemplated trial is always worth considering. This is because the situation has an agreeable 'heads I win' aspect. There are two possibilities. On the one hand, the two factors may turn out to interact. In this case, knowledge of the interaction is essential to the interpretation of the results and this can only be obtained with the factorial treatment structure. Alternatively, the two factors may act additively. In this case, when measuring the effect of either one of the factors all the subjects in the trial can be used—one has, as it were, two trials (one on each of the factors) for the price of one.

Breast feeding and urinary infection

The debate about the significance of the infection risk to bottle fed babies compared with breast fed has gone on for many years and shows no sign of abating. A recent study from Naples (Alfredo Pisacane and colleagues, *Journal of Pediatrics* 1992;**120**:87–9) points to a protective effect of breast feeding against urinary tract infection. Over a 14 year period (1976–89) they diagnosed urinary tract infection (more than 100 000 colonies per ml of a single bacterial species in bag urines) in 128 babies aged 6 months or less. For each baby a control of the same age and sex was chosen from among ward admissions for acute illness other than urinary infection, diarrhoea, or respiratory infection. Sixty four (50%) of the cases and 93 (73%) of the controls had ever been breast fed and 16 (12%) of cases and 56 (44%) controls were breast fed at the time of admission to hospital. Babies who had been breast fed at any time had a relative risk of urinary tract infection of 0·38 (95% confidence intervals 0·22 to 0·65) compared with those who had never been breast fed. Comparing those breast or bottle fed at the time of admission the relative risk was 0·18 (0·009 to 0·36).

I'm always suspicious of trials which go on for many years but this does seem to be the first real evidence that breast feeding may protect against urinary tract infection in young babies.

ARCHIVIST

LETTERS TO THE EDITOR

Asthma: a follow up statement from an international paediatric asthma consensus group

Sɪʀ,—We read with interest the follow up statement from an international paediatric asthma consensus group[1] We are surprised that the authors are not more emphatic about the value of peak flow monitoring in recognising severe episodes of asthma The authors state that patients should 'understand the use of peak flow meters' and that 'action plans should . . include instruction on the signs that indicate worsening of asthma'. Comparable guidelines for adults have been much more explicit about the use of peak flow meters in the recognition of severe episodes of asthma.[2 3]

Every asthmatic child over 5 years old who attends our outpatient clinic is given a peak flow meter. We teach families that they should identify their child's best peak flow reading We then give them a 'danger' figure (usually 60% of their best reading) and tell them to come to our accident and emergency department if the peak flow falls below that figure and does not improve promptly with bronchodilators. We find the asthma card supplied by the National Asthma Campaign to be useful This card has separate sections for noting the child's best and danger peak flow levels.

In a study of the value of home peak flow monitoring we have interviewed 58 families attending our clinic. Fifty four families knew their child's best and danger peak flows to within 20% of the actual values and knew what to do about readings below the danger level. Four families either did not use the peak flow meter or had too poor a knowledge of their child s best and danger peak flow readings for the meter to be useful.

Most families find the concepts of best and danger peak flow levels helpful. The proportion of asthmatic children attending a clinic who have a peak flow meter and whose families know their child's best and danger peak flow levels is a useful performance indicator and can be audited.

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Beta glucuronidase and hyperbilirubinaemia in breast fed infants of diabetic mothers

Sɪʀ,—We read the paper of Sirota *et al* with interest.[1] They suggest, after a study of 10 breast fed infants of diabetic mothers (IDM) and their mothers plus 10 infant and mother controls, that the high concentration of β-glucuronidase in breast milk of diabetic mothers is an additional important cause leading to hyperbilirubinaemia in their breast fed babies. We were concerned about problems that may limit successful breast feeding in our hospital, and identified exaggeration of physiological jaundice as a major problem. Following the work of Gourley and Arend,[2] we aimed to determine if a relationship existed between the concentration of breast milk β-glucuronidase and the degree of early (first week) neonatal jaundice. Our study showed no relationship (r=0·12, p=0·4) between them in 55 healthy, full term infants who were breast feeding satisfactorily in baby and mother pairs on the third to sixth postnatal day.[3] There were no IDM Mean (SD) concentrations of breast milk β-glucuronidase and serum bilirubin were 387 (189) Sigma/units and 192 (108) μmol/l respectively. We felt that breat milk β-glucuronidase could not directly account for the exaggerated early neonatal jaundice seen in breast fed babies

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Use of the polymerase chain reaction to detect rhinovirus in wheezy infants

Sɪʀ,—We were interested in the report of the use of DNA amplification techniques applied to throat swabs taken from children with varicella zoster.[1] We have used similar methods to detect rhinovirus in samples taken from the nose in wheezy infants.

Rhinovirus infection is classically associated with the upper respiratory tract, being the major cause of the common cold. Community based studies in the 1970s have shown that rhinovirus infection was also frequently responsible for exacerbations of wheezing in susceptible children.

Detection of rhinovirus is notoriously difficult because of the existence of the many immunologically distinct serotypes which excludes the use of immunological assays. Some of the serotypes also grow poorly in tissue culture. This has been highlighted by the large study in Tuscon where rhinovirus was isolated fewer than five times out of 348 episodes of lower respiratory illness, despite the fact that they achieved a very high overall viral isolation rate of 66%.[2]

Recent techniques have been described which utilise the polymerase chain reaction (PCR) to amplify and detect RNA from rhinovirus.[3] With experience the method is rapid, sensitive, and reliable.

Nose swabs were taken and nasal lavage performed on infants hospitalised with wheezing secondary to an upper respiratory tract infection. Lavage was carried out with phosphate buffered saline and 200 μl aliquots were stored at −70°C.

PCR was performed after RNA extraction from nasal washes and reverse transcription. The two primers used, OL24 (5'CTACTTTGGGTGTCCG 3') and OL68 (5' GGGACCTTCCACCACCANCC 3'), bind to highly conserved sequences found in all rhinoviruses and in each case give a fragment of approximately 550 nucleotides A positive result was indicated by the presence of a DNA fragment of this size after subjecting the PCR amplified sample to agarose-gel electrophoresis. Although the sequences are also present in enteroviruses, here the fragment size generated by PCR is rather larger (approximately 690 nucleotides) and so this method enables differentiation between the viruses. All the positive samples gave the rhinovirus specific fragment.

There were 43 episodes recorded in 34 children, aged between 4 weeks and 2 7 years (average 8·8 months). Successful assaying was only possible in the lavage samples. Rhinovirus was detected in three out of 23 episodes that were negative for respiratory syncytial virus. In all three cases, rhinovirus was no longer present in the nose when the children were healthy, implying that it had not been present as a commensal organism. No child was positive for both rhinovirus and respiratory syncytial virus. In one case, a 6 month baby wheezing with respiratory syncytial virus was accompanied by her 2 year old brother who also had a viral wheeze, only his was due to rhinovirus.

In conclusion, PCR techniques can be successfully used to detect rhinovirus in the nose of infants who have an exacerbation of wheezing at the time of an upper respiratory tract infection.

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BOOK REVIEWS

The Diary of a Teenage Health Freak. By Aidan MacFarlane and Ann McPherson. (Pp 154; £2 99 paperback.) Oxford University Press, 1991 ISBN 0–19–286083–6.

I am at the age where I can tolerate most adults and in a job which has taught me to enjoy most children. I'm also at that point in family life where I wish that there was nothing in between the two extremes of existence.

Aidan MacFarlane and Ann McPherson must be much more tolerant. Taking a leaf out of Sue Townsend's Adrian Mole format, they have produced a health education guide for teenagers cunningly disguised as a hypochondriac's daily diary I gave it to two teenagers consecutively to write the review for me; neither would take time off long enough from fixedly gazing at a TV screen to do so I have therefore been forced to read something written in language acceptable to 15 year olds. Me, an Oxbridge graduate with 'O' level Latin and deeply held prejudices about the slow death of the English tongue. I don't know Ann McPherson but her coauthor is a working colleague and had always struck me as a perfectly decent sort of individual, despite his attachment to a lap-top at all times He, for one, therefore deserves boundless praise for having to live with ranges of penile length and all the street names for commonly used illegal drugs for however long this book gestated.

All books dealing with a foreign species need interpreters, as the best anthropologists well know. The authors credit 4th year pupils in two Oxfordshire schools, their hard pressed teachers, and their own six children (separately, that is, not together) and their friends, who 'often surprised us and sometimes horrified us by their revelations concerning sex, drugs, alcohol, divorce and much else besides'.

The Diary of a Teenage Health Freak merits the best seller list. Teenagers continually surprise me by the depth of confusion and desire for knowledge, lurking underneath apparently impenetrable hostility and arrogance, especially about matters to do with their bodies and with health.

Most health education is not written in teenage-friendly language and when it is it tends to be condescending. MacFarlane and McPherson avoid both these pitfalls. The style is sufficiently engaging to hook the toughest of adolescents and the messages slip in non-threateningly If you are over 20 it's a lot less readable than *Viz* magazine but it's a worthy present for any relative or acquaintance aged 12 to 16 and there's always the hope that older thugs and layabouts might light on it by chance.

It would look well on the shelves of the ward adolescent unit library and any reader of *Archives* who is responsible for producing health education literature locally would do well to study its style.

HARVEY MARCOVITCH
Consultant paediatrician

Pediatric Outpatient Procedures. Edited by Jacob A Lohr. (Pp 383, $49·50 hardback.) J B Lippincott Company, 1991 ISBN 0–397–50897–2.

If you are into mediaeval torture, read on. This comprehensive approach to investigative and therapeutic techniques specialises in methods of restraint. The most alarming of these is the commercially available strapping for the restraint of the child undergoing gastric lavage (fig 23–3). That it is practical I have no doubt but I am concerned about the punitive nature of the treatment. Whether this should be an outpatient procedure at all is also questionable

However, brutality aside, the book is an extremely useful aid to paediatricians, paediatric nurses, and general practitioners It clearly outlines the indications and contraindications for just about any outpatient procedure you may need including an excellent chapter on resuscitation and one on dental procedures. For each procedure it then lists the equipment necessary and gives a detailed description of the method with a final comment on possible complications. This book is very user friendly and all written descriptions are backed up by clear diagrams or photographs.

I was surprised that there was no mention of jejunal biopsy in the gastroenterology section but I am sure that this is a reflection of how rare coeliac disease is in North America. I think that ear piercing could have been omitted as I know no one in this country with the time or inclination to pop a couple of studs into a child's ears in outpatients! There are several procedures in this book which are underused in this country and may be of great benefit in certain circumstances. Intraosseous infusion is one such example This is a simple and safe way of giving fluids to a shocked child and avoids wasting precious time looking for veins.

Although, as the editor states, nothing can replace the 'see one, do one, teach one', approach we all know that there are times when one of those three vital steps is missing from our training. I know that I shall find this book useful not only as a reminder before undertaking the less common practical procedures but also to ensure that I teach procedures accurately In fact I feel that every paediatric casualty and day care department should have a copy.

SUSAN LAURENT
Paediatric senior registrar

Adolescent Medicine. By Victor C Strasburger and Robert T Brown. Churchill Livingstone, 1991 (Pp 569; £29·95 paperback) ISBN 0–316–81872–0

Is adolescence really necessary? The authors think not, but that it is a 'culture phenomenon' of Western society not found in primitive communities (see page 400) Do we need a textbook of adolescent medicine?

This practical book is written by two American paediatricians both of whom head divisions of adolescent medicine There are sections on normal growth and development, the adolescent's initial interview, common medical problems, the adolescent with chronic illness or disability, sex, adolescent sports medicine, adolescent psychology and substance abuse, with a short section on related legal issues in America.

Despite the book's conciseness there are familiar throw away insights—why do 13 year old girls at college dances go to the 'bathroom' (American for toilet) four at a time? The section on the initial interview with its boxes (page 31) is very welcome to all of us confronted by a sullen teenager in a busy clinic. The adolescent's need for confidentiality, dignity, and relative freedom to consent is emphasised throughout and is rather different from the conventional paediatric approach, although it is in line with the spirit of our new Children Act The account of chronic fatigue (ME) syndrome is the best I have seen anywhere, giving clear criteria for diagnosis. Acne and sexually transmitted diseases are presented in an unusually accessible manner. The chapter on the adolescent growing up with chronic disability was thought provoking. Contraception, not home ground for most paediatricians, is well discussed. Strangely, the teenage mother is not mentioned

The style is didactic and selective The section on adolescent psychology settles for the normal, suicide, depression, acting out, psychosomatic disorders, and disturbances of eating. This is a practical book, easy to access with many lists and tables There is an occasional black and white diagram and flow charts for management. References are plentiful, mainly American and up to 1990, and are separate from the lists of suggestions for further reading

The book does not define adolescence Any chronic condition imposing lifestyle restrictions is liable to be stormy in adolescence, so it is surprising to see no mention of coeliac disease, cystic fibrosis, or metabolic disorders. Diabetes mellitus was well covered, although there was little that related specifically to adolescence.

I know of no other book which covers this field so succinctly It does achieve its stated aims of being 'a time-saving review of the most common adolescent conditions' which is practical and immediately available. It should be useful to a range of doctors and others meeting adolescents in the health service. Perhaps there is an even greater need of this book in this country where there is so little in the way of specialised facilities for adolescents It encourages doctors as well as parents to be accessible, accepting and available, but not overinvolved or possessive.

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Ambulatory Pediatrics. Edited by Morris Green and Robert J Haggerty. (Pp 651, £41 hardback.) W B Saunders Company, 1990 ISBN 0–7216–4240–3

It makes a pleasant change to read a book that concentrates on the outpatient care of children, as so many paediatricians spend much of their working time in the clinic. Although this book is intended for the North American office paediatrician, there is much of interest to the doctors working with children this side of the Atlantic

Many new chapters have been included in this fourth edition such as maternal depression, adolescent risk taking, physical fitness, AIDS, the impact of chronic illness on siblings, and home care. The text is divided into five sections and 116 chapters from half to 20 pages in length, with few illustrations. There are over 100 contributors The theme is adaptation and each section relates to a different kind of adaptation This makes things unnecessarily obscure and simpler headings indicating the subject matter would have been clearer—that is, epidemiology and environmental influences, preventative medicine, acute illnesses, chronic diseases, and the organisation of the practice.

There is strong emphasis on the social, emotional, and psychological aspects of child health. Chapters are devoted to family matters such as working mothers, day care facilities, life events, and children and television. The average North American preschool child watches 28 hours of television a week[1] It is suggested that paediatricians should recommend an hour's television a day for their young patients. The adverse effects of poverty, lack of health insurance, and poor housing are referred to repeatedly. There is even mention of a newly described condition called the homeless child syndrome.

As always, there are differences of emphases in the practice of medicine in the United States compared with the United Kingdom. Nineteen pages are devoted to sexually transmitted diseases but the whole of physical and sexual abuse is covered in only six. I was not impressed to find meningococcal infection deeply buried in a very theoretical section on purpura.

Despite these criticisms this is a readable book with a different slant from most British texts. It should be useful to general paediatricians, general practitioners, and trainees in both fields I recommend it to the practice or departmental library.

M CUMMINS
Consultant paediatrician

Color Atlas of Child Sexual Abuse. By David L Chadwick, Carol Berkowitz, David Kerns, *et al* (Pp 163; $25·50 paperback) Year Book Medical Publishers 1991 ISBN 0–8151–1605–5

The back cover of this slim paperback sets out the authors' aims: to provide diagnostic assistance, to prevent missed diagnoses of abuse, and to avoid over reporting of abuse. It claims to be a practical guide for use in office, clinic, and emergency room settings by health care professionals. Does it succeed?

The bulk of the book contains over 100 colour plates of children's genitalia and anuses supported by details of each child's age and sex, examination method, and a brief clinical history. The introduction illustrates examination techniques and the three sections then show normal findings, findings that 'commonly result from non-sexual or indeterminate etiology' and findings resulting from sexual abuse. This last section includes some dozen plates illustrating the clinical manifestations of selected sexually transmitted diseases.

Despite the comprehensive nature of the illustrations, one is left with feelings of incompleteness and unease about the use of this book by generalist 'health care professionals' to whom it is directed. Clearly detailed discussion of multidisciplinary assessment and management are outside the book's scope. However, important omissions are a diagrammatic key to the anatomical terms used in describing various physical signs and illustrations of any penile injuries. The plates showing lichen sclerosis atrophicus are also disappointing. On the positive side, the sequential illustrations showing healing are helpful, as are those showing normal variations in hymenal configuration

This is not a book from which the inexperienced doctor should seek reassurance about his or her 'diagnosis' when presented with a child with an anal or genital complaint, as it cannot replace discussion and advice from a more experienced clinician. Those who are regularly asked to examine children who may have been abused will find it a useful reference text.

HILARY SMITH
Consultant paediatrician in community child health

Disorders of Carbohydrate Metabolism in Infancy. Edited by Marvin Cornblath and Robert Schwartz. (Pp 416; £49·50 hardback.) Blackwell Scientific Publishers, 1991. ISBN 0–86542–137–4.

Clinical practice is a delicate balance between dynamic pragmatism and scientific certainty. As far as glucose homoeostasis is concerned, there has been a slow but sure shift towards the latter, attributable in considerable measure to the efforts of the editors of this book. The new, extensively revised edition is one of those rare books that is a must for every paediatrician because it contains a wealth of practical advice based on sound pathophysiology. It is written in concise, clinically oriented sections which deal with the whole spectrum of metabolic upsets where they are relevant to glucose homoeostasis.

It lays out clearly that which is certain and illustrates our complete ignorance of areas pertinent to everyday practice (dynamic pragmatism to the fore). The most telling of these is that there is still no agreement on the exact definition of hypoglycaemia after 30 years of research! The authors comment that a properly controlled prospective trial of plasma glucose concentration *v* neurodevelopmental outcome in newborn infants has never been done to define a 'safe' value. At a practical level, there is an excellent discussion on the problems of the poor precision of reagent strips for the diagnosis of hypoglycaemia. New sections have been included on the common problem of hyperglycaemia in the extremely low birthweight infant (or in their terminology 'the micropreemie') and transient neonatal diabetes mellitus is given a chapter of its own.

The book is divided into two broad areas, the first half is an update on hypoglycaemia (very useful for the research fellow starting on a project) with a particularly helpful section on the management of the infant with persistent severe hypoglycaemia. The second half contains separate chapters devoted to the special problems relating to glycogen storage diseases (we will have to revise what we teach the medical students: glucose-6-phosphatase is not that simple anymore), galactosaemia/fructosaemia (ranging from the molecular genetics to the clinical prognosis), and metabolic diseases which masquerade as hypoglycaemia (rare, but always a severe clinical problem). At the end of the book there is an excellent section on the substances which are known to interfere with the reliability of glucose estimations in the laboratory (frighteningly large). The references alone are worth the price!

ANIL MEHTA
Wellcome Trust research fellow

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References

- References must be numbered in the order they appear in the text and include all information (Vancouver style).

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Revised June 1992

Archives of Disease in Childhood 1992; 67:764

MMR x 2?

In Britain it is currently recommended that the measles, mumps, and rubella (MMR) vaccine be given only once, between the first and second birthday or at the time of the preschool booster for those not immunised in their second year. In most children, immunisation gives protection lasting for 20 years or more so such a policy successfully pursued with a high take up rate should see the elimination of the disease from a community. Why, then, has measles not disappeared from the United States where in 1989 there were more than four times as many cases as in the previous year and 40% of the affected children had been immunised? Two national advisory bodies, the American Academy of Pediatrics (AAP) and the Centers for Disease Control (CDC), have recommended routine reimmunisation for all children in order to combat the problem. The AAP recommends reimmunisation at 11 or 12 years and the CDC at 4 to 6 years of age.

A study done in Texas and reported in *Pediatrics* (Robert Wittler and colleagues, 1991;**88**:1024–30) throws further light on the subject. They obtained paired sera before and after repeat immunisation from 183 subjects aged between 4 and 20 years. Immunobiological measles susceptibility was defined as a fourfold or greater rise in measles specific IgG titre in the post reimmunisation sample and on that basis 10% of subjects were susceptible and therefore vaccine failures. Vaccine failure may be primary (no immune response) or secondary (initial immune response which wanes). After primary failure successful repeat immunisation should produce an IgM antibody response but there should be no such response after secondary failure. Using this criterion 28% of vaccine failures in this study were primary. As the immune response demonstrated by a fourfold rise in measles titre is evidence of susceptibility to *infection* but not necessarily to *disease,* the vaccine failure rate derived in this way is probably an over estimate. Previous estimates have varied between 2 and 10%.

In the present study, the main correlation with vaccine failure was age at first immunisation, the failure rate being some four or five times greater in those first immunised at under 12 months of age than in those first immunised at over 15 months. The British Department of Health recommends reimmunisation for children immunised under 1 year of age. Nevertheless, of the 18 measles susceptible subjects in the Texas study, only two had been immunised before their first birthday. Simply eliminating too early immunisation, therefore, is unlikely to solve the problem. Neither is reimmunising only those with a low measles IgG titre as, although such people are more likely to be susceptible, susceptibility was demonstrated in some with fairly high titres.

The question of optimal timing of the second dose is not settled. There is some suggestion from the Texas data that reimmunisation at the later age (11 or 12 years) might be more successful but the evidence is inconclusive.

The stated aim when MMR was introduced in Britain was to eliminate these diseases. American experience suggests that, at least in the case of measles, a single dose may not do so.

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Archives of Disease in Childhood 1992; 67: 765–769

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FETAL AND NEONATAL EDITION

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Annotations

Do we need an Apgar score?

In the 38 years that have elapsed since Virginia Apgar described a scoring system for the assessment of the condition of infants at birth, the Apgar score has achieved legendary status as the 'gold standard' outcome measure for countless studies. In light of modern perinatal practice, it is important to assess the value of the score – does it still measure what it originally intended to? Is the score being used appropriately? Can we improve on it?

Recording the Apgar score

The scoring system was designed to be made by an independent observer at one minute after delivery as an indicator of immediate newborn condition, in order to guide appropriate delivery room management.[1] To this a further score at five minutes is added, and it is common practice to record the score every five minutes or so while resuscitation continues. The Apgar score is therefore a shorthand method of recording the clinical condition of a newborn infant, relying on five signs – heart rate, respiration, muscle tone, reflex irritability, and colour – that should normally be assessed when deciding to proceed with a resuscitation.

In most situations the scoring is incorrect because the staff who have carried out the resuscitation generally make the assessment. In practice the record is made retrospectively and can only indicate what the attendants recall. This may be some considerable time after delivery should the child be intubated and ventilated to the intensive care nursery, the attending doctor being asked to complete the score some time later. One may speculate that the allocation of very low scores (0–3) may be better recollected than intermediate scores, though there is little evidence for this.

It is rare for a resuscitator to consciously use the full Apgar score to determine how resuscitation should proceed, as originally intended. The combination of respiratory effort, colour, and heart rate guides most people, although colour may contribute little to the assessment.[2] The final two items must then be estimated rather than assessed at the correct time. Even simultaneously recorded scores vary between observers: one case history based survey finding correct scoring in only 68% cases.[3]

The Apgar score makes no allowance for the present day practice of intubation, not widely performed in the early 1950s. How does one allocate a score for respiratory effort in a child breathing spontaneously but also receiving intermittent positive pressure ventilation? Can such a baby receive a score of 10? Our practice is to allow a maximum of 1 in this situation.

The application of the Apgar score to very preterm infants has also been questioned. Such infants frequently have low scores and may be assessed during active resuscitation or elective intubation. Reflex irritability, muscle tone, and respiratory effort may all be less pronounced in immature compared with mature infants.[4] Preterm infants with low Apgar scores tend to have higher pH values than similarly depressed term infants.[5] The five minute Apgar score is positively correlated with birth weight and is higher in small for gestational age infants compared with their appropriately grown counterparts.[6]

The problems associated with recording the Apgar score are thus easy to identify. Some can be overcome by better recording of data during resuscitation, perhaps using audio recording during resuscitation – an old idea[7] – and accepting differing cut off points or standards for very preterm children. Identification of the contribution of component scores for preterm children is required. The glaring defect in the practical measurement of the score is, however, its inherent inaccuracy between observers, something that may not be easily overcome.

Attempts to improve on Apgar's original score

There have been few studies which have evaluated the relative contribution of the constituent parts of the score. There are complex relationships between the various components of the score. Producing a weighted score removes the simplicity of the original[8] and there have been no successful attempts to replace the score with a viable alternative. In one elegant study the score allocated for colour was found to contribute little to the prediction of umbilical pH, arterial carbon dioxide tension, and base excess, in contrast to the other items.[2] The authors proposed that the score be used without colour, giving a maximum score of 8. Such a score would have the advantage of reducing the error that may be introduced in the assessment of dark skinned infants.[9] Perhaps this suggestion bears re-evaluation.

Relationship with other measures of fetal compromise

Much of the criticism that is levelled against the Apgar score is based upon the seemingly poor relationship that it has with other measures of perinatal compromise (fetal heart rate abnormalities, meconium staining of amniotic fluid, acidosis at birth) and the equally poor relationship it appears to now have with survival, neonatal hypoxic-ischaemic encephalopathy, or later neuromotor impairment. This criticism would have more weight if other measures of fetal compromise had any closer relationship with outcome.

Umbilical arterial or venous pH have been proposed as better markers than Apgar score, although there is little evidence that pH is any better.[10 11] The relationship between Apgar score and umbilical pH is not clear. Sykes and colleagues demonstrated a poor correlation except at the extremes of acidosis,[12] confirming an observation made as long ago as 1958.[13] None the less, studies have continued to explore this relationship: in one recent study 61% of children with low one minute Apgar score (<7) had a normal pH (>7·15); 74% of children with a low pH had a normal Apgar score.[14] Umbilical pH may explain only as little as 8% of the variance in one minute Apgar score.[15] In a further study, by five minutes after birth only 11% of acidotic infants had low Apgar scores and only 41% of those with low five minute Apgar scores were acidotic.[16]

A closer relationship with pH has been proposed if colour is excluded[2] and the Apgar score is measured immediately after birth,[-7] but each remains a poorly sensitive measure of the other. The correlation between Apgar score and umbilical pH may become reliable only in those severely depressed infants with very low pH values (<7·00) and very low Apgar scores (<3).[-5 18] It has been proposed that those chronically asphyxiated infants with a corrected metabolic acidosis, who do not respond to further hypoxic stress with increasing acidosis, may be at greatest risk and that the ability to respond to hypoxia with acidosis is a good prognostic sign.[11] It would appear therefore that acidosis and Apgar score are measures of different processes which at best appear to be only loosely related.

Abnormalities of the fetal heart rate pattern and the presence of meconium in the amniotic fluid are used to predict risk of asphyxia and to determine the management of labour. However, monitoring the fetus during labour may not improve the outcome.[19] Neither fetal heart rate pattern nor the presence of meconium are good indicators of umbilical pH or Apgar score. In one study, although the best correlate of pH was fetal heart rate pattern, it only explained 12% of the variance in pH. Mode of delivery and the presence of meconium were the best correlates of Apgar score but even with the addition of fetal heart rate pattern only 17% of the variance was explained.[15] Most of the variance in Apgar score, or pH for that matter, remains unexplained by abnormalities in the progress of the perinatal period as currently assessed.

Other markers of immediate neonatal condition, such as time to onset of spontaneous breathing/first breath or need for intubation suffer from the same disadvantages as the Apgar score and are likely to be less discriminatory, being single item measures and dependent upon maternal medication. They have not been systematically studied.

Relationship of Apgar score with neonatal and later outcome

The best clinical indicator that an infant has suffered significant asphyxial insult after birth is the neurological course over the days immediately after birth. The grade of postasphyxial encephalopathy (graded as mild, moderate, or severe[20]) is closely associated with a range of impairment ranging from early mortality, through severe impairment, to learning disabilities at school age.[21 22] Few studies that attempt to study fetal condition or compromise assess the neonatal or later progress of the infants.

In the absence of the provision of good neonatal resuscitation and follow on care directed at limiting damage from asphyxia, the low Apgar score may identify infants with a high mortality and morbidity.[22] In a recent study from Zimbabwe this would appear to still be the case: among 84 term newborns with five minute Apgar scores of 5 or less, 17 failed to establish respiration, 44 had moderate or severe hypoxic-ischaemic encephalopathy, and 42% died.[23]

Most studies of fetal condition and outcome, however, come from centres with highly developed perinatal services, where the predictive value of the Apgar score is less clear. In one study Apgar score, cord pH, and lactate all demonstrated poor sensitivity and positive predictive value for 1 year neurological outcome.[16] Other studies have failed to document associations with Apgar score of assessments made up to 17 years after birth.[24] The analysis of the antecedents of cerebral palsy from the National Collaborative Perinatal Project observed that a low Apgar score had to persist through to 20 minutes before an association could be found.[25] In contrast, studies of neonatal mortality, asphyxial encephalopathy, or neurological impairment may identify a greater proportion of children with low Apgar scores among index groups, compared with controls. Since its first description the predictive effect of the Apgar score has been considerably weakened by the institution of prompt and effective neonatal care.

It is unlikely that the prediction of neonatal morbidity after perinatal asphyxia will be made by any single measurement. The use of blood lactate, creatine kinase, and other metabolic markers has not been attended with much success. One group has recently proposed a scoring system for neonatal organ dysfunction after perinatal asphyxia using a combination of the five minute Apgar score, an arterial base deficit measurement in the first postnatal hour, and the result of fetal monitoring.[26] This composite score achieved a sensitivity of 94% and a specificity of 81%, far better than any single measure. Further prospective studies are needed to confirm this. It would seem logical that a selection of markers combined will prove more predictive than any one alone.

Should we still record the Apgar score?

In a leading article in 1989, the *Lancet* called for the Apgar score to be 'pensioned off.'[27] There was no attempt to suggest a replacement, nor how one should record the state of the infant at birth. I suspect that much of the concern about the Apgar score in the literature results from incorrect interpretation of a low Apgar score as being synonymous with asphyxia, which it is not, and the use of this erroneous opinion in medicolegal work.

Although we should remain cautious in our interpretation of an individual Apgar score, it has value as a descriptor of the condition of the infant at birth. It is not by itself a useful outcome measure, nor does it predict the further progress of the infants reliably. We should maintain vigilance that it is measured as accurately as possible in each delivery suite and continue to search for other measures that may better indicate neonatal condition immediately after birth. Although imperfect, it would seem a little premature to pension the Apgar score off yet.

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Metabolic acidosis in newborn infants

The maintenance of a proton (hydrogen ion) concentration within a relatively narrow range is essential for normal cellular function. This is as true for newborn infants as it is for older children and adults. Although very large quantities of protons are produced during normal metabolism by the oxidation of substrates to carbon dioxide, hydrolysis of adenosine triphosphate and reduction of adenosine dinucleotides, these are effectively removed by associated reactions. In health net production of protons results primarily from the catabolism of sulphur-containing amino acids and hydrolysis of nucleic acids in the diet. In order to maintain a normal pH, hydrogen ions are buffered by extracellular and intracellular proteins, inorganic phosphate, and bicarbonate. Net loss of protons from the body results from loss of carbon dioxide in expired gas (with hydrogen ions being effectively lost to water) and from the excretion of dihydrogenphosphate and ammonium ions by the kidney. Reabsorption of sodium bicarbonate by renal tubules, although not resulting in any net loss of protons, is also important in maintaining normal acid-base balance.

Respiratory acidosis in the newborn period may be due to disorders such as respiratory distress syndrome, transient tachypnoea of the newborn, and meconium aspiration, and results from the reduction in carbon dioxide excretion by the lungs with a subsequent increase of carbonic acid. Metabolic acidosis, defined as the accumulation of non-carbonic acid equivalents, arises from excessive production or inadequate excretion of hydrogen ions or from an increased loss of bicarbonate. In practice metabolic acidosis may result from birth asphyxia, cold stress, hypovolaemia, sepsis, congenital heart disease (particularly hypoplastic left heart syndrome, coarctation and interruption of the aortic arch), renal disease (for example polycystic kidneys, obstructive nephropathies, renal tubular acidosis), maternal acidosis, and inborn errors of metabolism.[1] Acidosis has also been reported in newborn infants with imperforate anus and rectovaginal fistula,[2 3] neonatal diabetes,[4] benzyl alcohol poisoning,[5] saline flushes,[6] parenteral nutrition,[7] and in those fed with casein formulas[8] or with goats' milk.[9]

Although the mechanisms by which acidosis causes harm are not fully understood, severe acidosis is associated with disturbances in cerebral blood flow, periventricular haemorrhage, leucomalacia, increased peripheral vascular resistance, and decreased myocardial function.[10 11] A fall in cardiac output and poor tissue perfusion may increase tissue hypoxia and lead to worsening acidosis.

Preterm infants are more susceptible to many disorders that cause metabolic acidosis such as cold stress, infection, and respiratory distress syndrome and have a reduced capacity to prevent and correct acidosis. Although the kidneys will respond to an acid load in a qualitatively similar manner to term infants, immaturity of renal function results in a reduced glomerular filtration rate, lower tubular bicarbonate threshold, and increased urinary sodium loss.[12] Additionally any concomitant respiratory disease may restrict the ability of the preterm infant to compensate for a metabolic acidosis by increasing the excretion of carbon dioxide.

Inborn errors of metabolism

Although individually uncommon, inborn errors of metabolism are not a rare cause of metabolic acidosis in the newborn and are more likely where there is consanguinity or a family history of unexplained neonatal deaths or illness. Their presentation is, however, usually non-specific, and unless appropriate investigations are undertaken the correct diagnosis may be missed. Characteristically, but not exclusively, infants with an inborn error of metabolism are born at term and are initially well. In preterm infants acidosis is much more likely to be secondary to other causes such as septicaemia but the possibility of an inherited metabolic disorder should still be borne in mind. The main groups of inborn errors that may present with a severe metabolic acidosis are (i) defects of pyruvate metabolism and the mitchondrial electron transport chain, (ii) the organic acidaemias, and (iii) defects of gluconeogenesis.

Investigations

In the majority of sick infants a full infection screen and liver function tests will usually be undertaken and concentrations of arterial blood gases, blood glucose, and plasma electrolytes are measured. A metabolic acidosis is evident from a low plasma bicarbonate, a low arterial carbon dioxide tension, and a low arterial pH. The history, clinical examination, and the results of these initial investigations will normally be sufficient to determine the cause or to indicate which additional investigations are necessary. In infants where the acidosis is unexplained, particularly severe, or persistent, or where there is a large anion gap, the possibility of an inborn error of metabolism should always be considered and further investigations should then include measurement of concentrations of blood lactate and ammonia, plasma amino acids and urine amino acids, organic acids, ketones, and reducing substances. Assays on specific tissues samples will be dependent on the results of these. A directory of laboratories in the UK and Northern Ireland undertaking specialised metabolic investigations is available.[13]

Lactic acidosis

Although a raised blood lactate concentration is most often secondary to tissue hypoxia it is also found in inherited disorders of hepatic gluconeogenesis (glucose-6-phosphatase deficiency, glucose-6-phosphate translocase deficiency, and fructose-1,6-bisphosphatase deficiency), disorders of pyruvate metabolism (defects in the pyruvate dehydrogenase complex and pyruvate carboxylase deficiency), and functional defects in the mitochondrial electron transport chain. It may also be associated with organic acidaemias. Gluconeogenic disorders are associated with hypoglycaemia. In congenital lactic acidaemias symptoms may be apparent from birth, the blood lactate concentration is usually above 5 mmol/l, and an anion gap is present that may be accounted for by the hyperlacticacidaemia. In contrast to lactic acidosis secondary to tissue hypoxia, ketosis is present and the acidosis persists even when there is adequate cardiac output and tissue perfusion.[14] Infants with pyruvate dehydrogenase deficiency may be dysmorphic.[15] The biochemical diagnosis of these disorders, and interpretation of results, is particularly complex and undertaken by only a few specialised laboratories. Despite significant advances in the investigation of infants with congenital lactic acidosis in many the underlying metabolic abnormality remains unknown.

Organic acidaemias

Most children with an organic acidaemia are born at term and are well for the first one to four days of life. The onset of illness is not necessarily related to the start of feeding but may be triggered by endogenous protein catabolism. There is then a rapid deterioration beginning with poor feeding, irritability, and lethargy proceeding to apnoea and coma. On examination there may be dehydration, respiratory distress, central hypotonia, and limb hypertonia. Initial investigations will show a severe metabolic acidosis, ketosis, and usually hyperammonaemia and hypocalcaemia. Neutropenia, thrombocytopenia, and hypoglycaemia or hyperglycaemia are often found. The most common of the organic acidaemias, propionic, methylmalonic, and isovaleric acidaemia all present in this way, although variants with residual enzyme activity may not become unwell until later. Other rarer organic acidaemia in which metabolic acidosis may occur in the newborn period include 3-methylcrotonyl CoA carboxylase, 3-hydroxy-3methylglutaryl CoA lyase, holocarboxylase synthase, electron transfer protein (ETF) or ETF:ubiquinone oxoreductase, succinyl CoA:3-ketoacid CoA transferase, and glutathione synthetase deficiency. Maple syrup urine disease (keto acid branched chain decarboxylase deficiency) is often through to present with metabolic acidosis but this is rarely significant, although ketosis is generally found.[16] The diagnosis of an organic acidaemia is made by finding characteristic organic acids in the urine on analysis by gas chromatography linked to mass spectrometry (GCMS). This investigation is now available in most regional centres and a collection of urine for GCMS should be routine for all infants with an unexplained metabolic acidosis.

Other inherited metabolic disorders may also be associated with acidosis – for example salt losing forms of congenital adrenal hyperplasia (21-hydroxylase, 3β-hydroxysteroid dehydrogenase, and 20,22 desmolase deficiency). Metabolic acidosis may be found in galactosaemia (as a consequence of renal tubular acidosis) but liver failure is likely to be predominant. Urea cycle disorders are often initially associated with a respiratory alkalosis, however, as infants deteriorate acidosis may develop.[17]

Treatment

The treatment of neonatal metabolic acidosis consists of general supportive care and specific measures dependent upon the cause. Treatment of hypothermia, hypovolaemia, hypoxia, and electrolyte disturbances will usually correct metabolic acidosis secondary to asphyxia or poor tissue perfusion. Intravenous antibiotics should be given until sepsis has been excluded. Many infants will require ventilatory support. The morbidity and mortality for those infants with potentially treatable disease is likely to be significantly improved by skilled neonatal intensive care. The use of intravenous sodium bicarbonate to correct metabolic acidosis is controversial. There have, however, been no prospective trials of its use in newborn infants. It is considered by some to be unnecessary and even harmful, leading to changes in cerebral blood flow and paradoxically to increased cerebrospinal fluid or intracellular acidosis,[18] although provided that carbon dioxide can be effectively removed in expired air (by assisted ventilation if necessary) it will lead to a net loss of protons to water. If bicarbonate is used then it is important that the infant's ventilation is adequate, and hyperosmolar solutions should be diluted 1:2 to 1:4 with water and infused slowly over several minutes. In inborn errors of metabolism acidosis may lead to continued protein breakdown with further accumulation of toxic acidotic metabolites and sodium bicarbonate should be given. Glucose infused at a rate of up to 10 mg/kg/minute may inhibit protein catabolism in babies with inborn errors of metabolism and this effect will be further augmented by the addition of a continuous infusion of insulin, starting at 0·01 U/kg/hour, provided that the blood glucose concentration is satisfactory. In order to give sufficient glucose, but to prevent overhydration, particularly where there is renal impairment, concentrations in excess of 10% may be necessary. These are irritant to peripheral veins and should, if possible, be given via a central venous catheter. There are, however, limitations on the quantity of fluid that can be safely given and hypernatraemia may result from large quantities of sodium bicarbonate infused. In such cases it may be necessary to use peritoneal dialysis, haemodialysis, or haemofiltration to remove toxic metabolites and fully correct the acidosis.[19–21]

A number of inborn errors of metabolism are partially or wholly corrected by treatment with pharmacological amounts of the specific cofactors, but with the exception of holocarboxylase synthase deficiency where biotin should be given, those presenting acutely in the newborn period are unlikely to be responsive.The infusion of L-carnitine (up to 50 mg/kg/hour during acute illness) has been shown to increase the removal of toxic acyl CoA metabolites in patients with organic acidaemias,[22] but the high production rate of these metabolites may be far in excess of the infused carnitine,[23] and the efficacy of carnitine treatment in acute metabolic decompensation remains unproved. In isovaleric acidaemia, glycine (250–500 mg/kg/day) significantly increases the excretion of isovalerate as isovalerylglycine.[24]

Conclusion

Metabolic acidosis is common in the newborn infant. It is most often secondary to disorders resulting in hypoxia or poor tissue perfusion and will be corrected by the appropriate treatment for these conditions. It is, however, important for those caring for newborn infants to be aware that metabolic acidosis may be a result of an inborn error of metabolism and for specific investigations to be undertaken earlier rather than later. A correct diagnosis is important not only for appropriate treatment to be given but also to allow genetic advice to be offered to families including prenatal diagnosis for future pregnancies.

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Archives of Disease in Childhood 1992; 67: 770–774

ORIGINAL ARTICLES

Fetal abnormality: an audit of its recognition and management

Northern Regional Survey Steering Group

Abstract

A voluntary survey set up by local clinicians has documented all lethal abnormality in a geographically defined area of northern England where there were 361 037 registered births between 1982 and 1990, and monitored the incidence of all significant physical abnormality since January 1984. The survey aims to maintain a register of all pregnancies where an abnormality is suspected before birth, and those where an abnormality is only identified after birth, together with a record of how the diagnosis was established. Information on management and outcome a year after birth is also collected.

Nearly half the total decline in perinatal mortality in the region between 1982 and 1990 is accounted for by an increase in the antenatal recognition of lethal abnormality, isolated hydrocephalus, or a neural tube defect and subsequent termination of pregnancy. Although the reporting of many non-lethal conditions was incomplete during the pilot study in 1984, it has become progressively more complete since then. The number of cases confirmed postnatally varied little between units between 1985–9, but audit showed that the proportion recognised antenatally varied fivefold for reasons unconnected with unit size or the amount of antenatal ultrasound work done. For a number of serious conditions more than 10% of all antenatal diagnoses were completely wrong.

Survey data are, for the first time, making it possible to monitor the accuracy of the ultrasound-based screening and diagnostic services for identifying specific fetal abnormalities. They are also providing clinicians with an invaluable confidential database of a whole region's collective experience of dealing with complex fetal abnormality.

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Accepted 9 March 1992

Antenatal ultrasound screening, and other techniques for assessing fetal wellbeing, have developed very rapidly in the last 10 years. Sonar screening has been bringing to light abnormalities that had not previously been recognised before birth, but little was known about the reliability of prenatal recognition in routine clinical practice. False positive and false negative diagnoses are almost inevitable with any newly developed screening test, but the only available information on these risks was coming from a small number of national referral centres with a concentration of specialist experience but an ill defined catchment population. Equally little was known about the efficacy of the services available at district level or the impact the services were having on pregnancy outcome.

A voluntary, collaborative, mortality survey in the region had shown that a fifth of all perinatal death, and a third of all later death in the first year, was due to fetal abnormality.[1] Spurred by the success of that continuing study, the regional specialist subcommittees of the regional medical committee agreed to launch a parallel survey of fetal abnormality in order to address some of these questions. Our conclusions, based on data collected since the launch of the full survey in 1985 supplemented by information on lethal abnormality for the period 1982–4, are summarised in this paper.

Methods

The Northern Regional Health Authority, with a population of approximately three million, covers the counties of Northumberland, Durham, Cumbria, Cleveland, and Tyne and Wear. It is served by 19 consultant staffed maternity units and five small independent general practitioner units, responsible for delivering 40 000 babies each year. Very few of the mothers resident in the region receive any of their maternity care outside the region either in Scotland, Yorkshire, or the North Western Regional Health Authority. All the 19 units now have comprehensive antenatal ultrasound facilities (although the way these are structured varies widely) and there is also a regional referral service available to consultants anxious to obtain a 'second opinion'.

DATABASE

The survey aims to collect confidential information on all babies with a significant congenital abnormality born since December 1984 to mothers resident in the Northern Regional Health Authority at the time of delivery (even if delivery took place outside the region). The survey is interested in all suspected fetal abnormality, even if no abnormality is confirmed after delivery, and in any significant abnormality identified for the first time after birth. A description of how the survey operates was recently given at a study group organised by the Royal College of Obstetricians.[2]

Cases are generally notified by the consultant first made aware of the diagnosis (usually an obstetrician, paediatrician, paediatric surgeon, or radiologist) or their office staff. Other cases are notified by the cytogeneticists and pathologists. Necropsy data are usually available on file for children who died, and information on management and outcome (including disability) at 1 year of age in those who survived. Duplicate notification is not a problem because there are built-in mechanisms to prevent registration being duplicated – such reports often serve to provide further information on the progress of the cases known to the survey, and help to ensure complete surveillance.

CONFIDENTIALITY

No information capable of identifying any individual doctor or patient is transferred to the survey's computerised database. Postcode data and information on where each individual patient was originally booked for delivery are shown on certain of the confidential tabular check lists, but the steering group hold this information in strict confidence. Routine printed narrative listings of all cases with a specified diagnosis (or suspected diagnosis) and their outcome are available, however, on request, as are listings of all cases booking for delivery in a specified unit. The study has the approval of the ethics committee in each district.

VALIDATING THE SURVEY REGISTER

Cross checks were undertaken on all data collected during the first four years after the formal launch of the full survey.[2] Cross checks with the information forwarded on district health authority SD56 returns to the Office of Population Censuses and Surveys (OPCS) showed an almost complete match in respect of the number of registered births associated with a neural tube defect, isolated congenital hydrocephalus, exomphalos, rectal atresia, and cleft lip and palate.[3] For all other conditions notifications to the regional survey significantly outnumbered those submitted to OPCS. Others have reported similar findings.[4] Further confidential cross checks against the mandatory OPCS 'termination of pregnancy' returns,[5] against the regional health authority's database of all surgical activity, against the Registrar General's records of stillbirth and death in the first year of life, and against the region's own 'perinatal' mortality survey[1] have confirmed the completeness of case ascertainment.

LETHAL ABNORMALITY

For this report liveborn babies were classified as dying with a lethal malformation if they died as a direct result of a congenital abnormality within one week of birth, but stillborn babies and fetuses terminated because of abnormality were only classified as having a lethal defect if they had anencephaly, hypoplastic left heart syndrome, proved pulmonary hypoplasia[6] associated with hydrops or a major structural of skeletal abnormality (but not merely as a consequence of premature rupture of membranes), functional renal agenesis, or a chromosome abnormality seldom associated with sustained survival (such as polyploidy or an autosomal trisomy other than trisomy 21). Fetuses with a nuchal cystic hygroma or generalised lymphangiectasia were excluded from this analysis because almost all these fetuses die or abort spontaneously before 28 weeks' gestation.[7]

Results

An analysis has now been undertaken of all returns on babies born to mothers resident in the region between 1985 and 1989 inclusive.[2] There were 201 787 registerable births in that five year period. Information is available on all abnormalities identified at delivery or within one year of birth, and on the management and progress of all liveborn children in the first year of life. Using this information it is now possible to assess the efficacy of the antenatal techniques now being developed to screen for significant congenital fetal abnormality. Additional data on all perinatal deaths and on all pregnancies terminated because of proved fetal abnormality between 1982 and 1984 and in 1990 show the impact of antenatal diagnosis on perinatal mortality over a nine year period.

PERINATAL MORTALITY

The fall in perinatal mortality in the region between 1982 and 1990 (11·7 falling to 8·1 deaths per thousand births) paralleled that

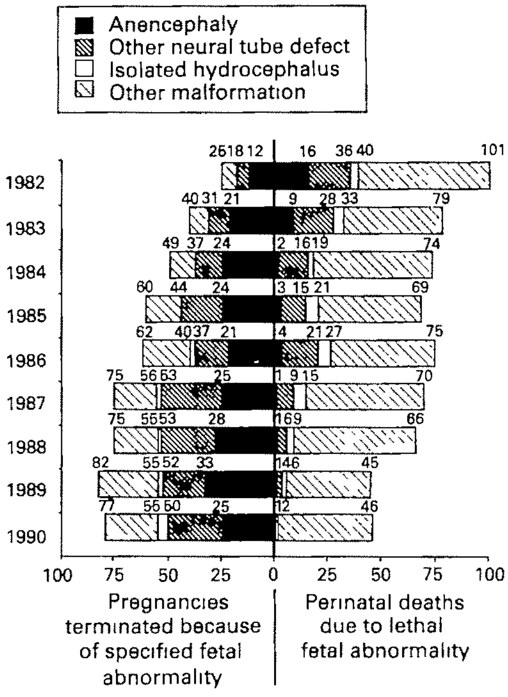

Figure 1 Neural tube defects, congenital hydrocephalus, and other lethal fetal abnormality in the Northern region 1982–90, their increasing antenatal recognition, and the impact of this on perinatal mortality

seen elsewhere in England and Wales. However while 23% (105/462) of all perinatal deaths in the region were classified as due to a congenital malformation in 1982, this was true of only 14% (46/331) of deaths in 1990. Almost half the decline in perinatal mortality seen in that nine year period is therefore due to a reduction in the number of registered births associated with a severe fetal abnormality,[1] and fig 1 shows that most of this latter decline is due to an increase in the number of pregnancies terminated because of fetal abnormality rather than a decline in the proportion of babies conceived (or, to be more precise, surviving spontaneously into the second half of pregnancy) with hydrocephalus, a neural tube defect, or a lethal abnormality as previously defined. The increased antenatal recognition of neural tube defects accounts for only part of the observed decline in registerable perinatal death.

THE ACCURACY OF ANTENATAL IDENTIFICATION

The table shows the extent to which certain of the commoner and more serious abnormalities are currently being recognised before birth in the Northern region. Serum α-fetoprotein screening is little used in the region at present, so the results show what was achieved by the routine clinical service using sonar screening supported by selective amniocentesis in a region where most primary screening is done in a range of relatively small district maternity units (although a regional referral service also exists). The antenatal recognition of many conditions did not change substantially over this time but the recognition of a few conditions, such as hypoplastic left heart, diaphragmatic hernia, and functional bilateral renal agenesis increased substantially.

The prospective nature and the size of this regional register make it possible, however, to assess not only the number of 'false negative' assessments, but also the risk of 'false positive' assessment. Thus, for example, although antenatal ultrasound assessment identified almost 30% of babies with duodenal atresia, there were quite a number of 'false positive' diagnoses and, as a result, given the relative rarity of duodenal atresia (one in every 10 000 births), positive antenatal ultrasound diagnosis was almost as likely to be wrong as right. For a number of other serious conditions more than 10% of all antenatal diagnoses were entirely wrong (table).

A pragmatic definition of what constitutes a false positive diagnosis was used for this analysis. A case was not so classified, even if the diagnosis made before birth was entirely wrong, if the error did not significantly alter prognosis or management. Thus a fetus suspected of having anencephaly was not, for this purpose, considered to have been misdiagnosed merely because the fetus was eventually shown to have severe cranial clefting due to an amniotic disruption sequence; neither was the fetus of a mother transferred to a referral centre for delivery because of a suspected diaphragmatic hernia merely because the baby was found to have cystic adenomatoid malformation of the lung at delivery. Other cases were more difficult to classify. For the present analysis a child antenatally suspected of having bilateral hydronephrosis due to pelviureteric junction obstruction was not classified as misdiagnosed if further investigation a month after birth revealed bilateral grade 3 reflux without obstruction, but another child with a similar antenatal diagnosis was so classified when posterior urethral valves and obstructive nephropathy were identified seven weeks after birth because this substantially changed the prognosis; a more precise antenatal diagnosis would also have altered immediate management after delivery as well. The consistent classification of antenatally suspected urological abnormality was often difficult[8 9] and always somewhat subjective; luckily few such problems of classification were encountered with other areas of antenatal diagnosis.

ANTENATAL RECOGNITION RATES

Over the five year period 1985–9 the number of postnatally confirmed fetal abnormalities reported to the survey rose slowly. The number of confirmed abnormalities for 1988–9 is at present 10% higher than for 1985–6, despite the fact that there has been more scope for abnormality to be recognised and reported in the older children. District rates also differ and, as the threshold for registration (designed to eliminate the inclusion of minor abnormalities) has remained constant, it has to be concluded that a degree of under reporting still exists.

One area currently being addressed is the reporting of children with cardiac anomalies (but no other congenital abnormality) only referred for specialist assessment more than four weeks after birth. Because the reporting of such cases is known to be variable and incomplete at present all such cases have been excluded from the analysis that follows. When such cases are excluded it is seen that between 1·1 and 1·7% of all babies are currently being reported to the survey (fig 2). Only one unit falls outside this range, and that is a unit from

Frequency and accuracy with which routine antenatal care detected certain selected fetal abnormalities before the start of delivery in the Northern region 1985–90 (prevalence and rate of detection per 1000 fetuses)

Nature of fetal abnormality	*Prevalence*	*Detection rate**	*Odds of being unaffected given a positive report†*
Central nervous system abnormality			
Spina bifida without anencephaly	1 03	605	1 40
Anencephaly	0 83	988	–
Isolated hydrocephalus	0 31	651	1 10
Isolated encephalocele	0 11	682	1 15
Holoprosencephaly	0 03	632	1 19
Other abnormality			
Abdominal wall defect	0 53	661	1 78
Diaphragmatic hernia	0·35	100	1 7
Functional renal agenesis	0 25	490	1 12
Non-immune hydrops fetalis	0 21	760	1 26
Lethal short limbed dwarfism	0 17	588	1 5
Bladder outlet obstruction	0 15	433	1 3
Hypoplastic left heart	0 15	194	–
Duodenal atresia	0 11	286	1 1 5

*Excluding the 1% of mothers who were not scanned before 24 weeks' gestation

†See text for a definition of what constituted a 'false positive' diagnosis

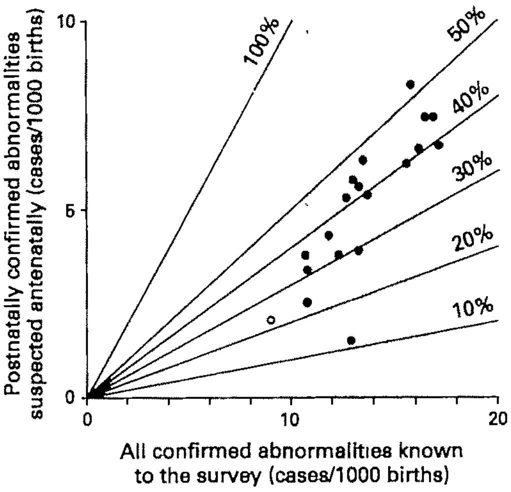

Figure 2 Significant postnatally confirmed fetal abnormality registered with the survey within one year of birth (excluding isolated cardiac abnormality only referred for specialist assessment more than four weeks after birth), and the extent to which such cases were identified before birth in the 19 consultant maternity units in the Northern region in 1985–9. Under reporting is suspected from one unit (marked with an open circle) because of the cross referral of patients into an adjoining region.

which some under reporting was to be expected because of the frequent cross referral of patients into an adjoining region both for obstetric and for paediatric care.

By contrast, the proportion of cases where a significant postnatally confirmed abnormality was suspected and reported before birth varied fivefold (fig 2), and checks after delivery have confirmed that this was not merely due to a failure to report the antenatal recognition of some problems to the survey. Maternity units in the region clearly vary in the success with which they identify fetal problems antenatally, and the variation does not seem to be linked to unit size, to the type of equipment in use, or to the amount of antenatal ultrasound work done. Units with a policy of offering every mother at least one full and detailed fetal ultrasound scan at about 18 weeks' gestation achieved very much higher 'pick-up' rates than other units that sometimes undertook more ultrasound work in total, but lacked a structured approach to the timing of this assessment. However this only accounted for a small proportion of the interunit variation.

Discussion

Unlike other European malformation registers,[10 11] this continuing survey has, from the outset, sought information on the outcome of late spontaneous miscarriage, and on the outcome of termination of pregnancy associated with fetal abnormality, as well as in all registered births where there is a significant congenital abnormality. The survey also collects information on how these diagnoses were made and on the management of the babies both before birth and for at least the first year of life after birth, together with information on the extent to which registered survivors are disabled or handicapped when 1 year old. Without comprehensive data of this nature, collected from a wide range of sources and carefully validated for accuracy, it will never prove possible to assess the efficacy of the antenatal and neonatal techniques now being developed to screen for significant congenital fetal abnormality (structural, metabolic, or genetic in origin) either during pregnancy or in early infancy.

Had the antenatal diagnostic ability of every unit in the region matched that of the best, a hundred more significant antenatal diagnoses would have been made in the region each year in the last five years. The three units with the highest rate of antenatally suspected abnormality (fig 2) achieved as high an antenatal recognition rate as in the recently reported prospective study over six years from teaching hospitals in Belgium[12] once allowance is made for differences in the way non-specific cardiac and renal tract dilatation were classified. A more recent study of 8700 mothers from Luton reported an even higher antenatal recognition rate (10 cases per 1000 births) in 1988 and 1989.[13] This may be a chance finding from a fairly small study sample, but it could also reflect the continuing secular rise in the rate of antenatal diagnosis seen in this region over the last six years. It certainly seems clear that maternity units should currently be striving to achieve an antenatal recognition rate of between eight and 10 postnatally confirmed cases per 1000 births in any community based population study.

A system that allows units to compare their antenatal pick-up rate with that of other comparable units should facilitate audit. A mechanism that ensures that those involved in antenatal assessment get to hear of the final outcome of those cases they did (and did not) suspect antenatally should further improve the quality of antenatal assessment. Given the multidisciplinary nature of much modern medicine this is never going to be easy, especially where a baby may well be diagnosed in one hospital, delivered in a second, and treated in a third before, perhaps, dying in a fourth. We believe our voluntary collaborative survey provides such a mechanism: the next aim must be to enhance the region's facilities for subjecting all fetuses where pregnancy is terminated to more comprehensive assessment after delivery,[14] and to speed up the operation of the survey's feedback loop.

The present survey is unique in providing information from which it is possible to calculate the risk of specific antenatal findings leading to a false positive diagnosis, as well as a false negative diagnosis. Furthermore, as abnormalities are registered with the survey as soon as they are suspected antenatally, and before the outcome is known, there is little risk of bias entering into the collection of these data. Several reports of the sensitivity and specificity of 'routine' antenatal ultrasound have appeared recently based on the study of a few thousand patients; no such study can hope to define the risk of falsely diagnosing the presence of any relatively rare condition antenatally with accuracy. The table shows that for certain conditions this risk is far from negligible. Nevertheless, it is clear that, while antenatal diagnosis is often imprecise, there have been relatively few cases where serious abnormality was suspected antenatally but no serious abnormality existed at birth. It is becoming clear, however, that minor degrees of tissue oedema, as seen in babies with a cystic hygroma, may resolve spontaneously. Mistakes have been made in attempting to determine whether any kidneys exist where there is severe oligohydramnios, and it is clear that no pregnancy should be terminated because of suspected renal agenesis on the basis of a single scan however carefully it is undertaken. The early diagnosis of hereditary neonatal polycystic kidney disease can be difficult because renal enlargement and distortion may become obvious only late in pregnancy. Minor renal tract dilatation is not always confirmed at birth, and the accurate antenatal assessment of many cardiac abnormalities is not yet always possible, particularly where fetal visualisation is poor. The recommendations of the Joint Study Group on Fetal Abnormalities are apposite here.[15]

Four hundred and seventy four pregnancies were terminated because of proved fetal abnormality between 1985 and 1989. This represents 1·4% of all the terminations undertaken on mothers resident in the region during this time. Two hundred and thirty five of these fetuses were classified as having a lethal abnormality (using the working definitions given earlier) and another 199 had spina bifida or isolated hydrocephalus (fig 1). Other terminations were undertaken for conditions that normally cause midtrimester fetal loss, such as cystic hygroma (n=22); the remainder had abnormalities that would have caused a varying degree of disability such as Down's syndrome (n=37), Klinefelter's syndrome (n=4), Duchenne muscular dystrophy (n=3), cystic fibrosis (n=3) or the like. Only 23% of the babies with a lethal abnormality had a condition currently detectable by chorion villus sampling. A comparison of these figures with OPCS data on termination of pregnancy[5] suggests that all but eight of the 147 NHS terminations undertaken for *any* reason after more than 19 weeks' gestation on mothers normally resident in the region were undertaken for proved fetal abnormality.

The value of perinatal mortality as a 'performance indicator' by which to monitor the quality of any maternity service is limited. Analyses of the type shown in fig 2 show one way forward. Information of this nature is now beginning to provide clinicians with qualitative and quantitative feedback on their antenatal screening services, and we believe that the cost of the present survey justifies itself on this count alone. Such information (see table) is also now beginning to help clinicians across the region to know how much weight to give to individual antenatal ultrasound observations.

This voluntary collaborative survey has only been made possible by the support of obstetricians and paediatricians throughout the region, and the active help of many consultant radiologists Radiographers have helped to secure case notification in many districts, and the part played by clinical secretaries also deserves recognition. The support of district medical officers and their staff, and the collaboration of the three regional cytogenetic laboratories, is also gratefully acknowledged

The continuing study is managed on behalf of all maternity unit staff in the region by a steering group comprising Mr A F J Atkins, Professor J M Davison, and Mr A S McIntosh, consultant obstetricians, Dr E Dillon, Dr T G Girdwood, and Dr P G Rose, consultant radiologists, Mr J E S Scott, paediatric surgeon (chairman), Dr S Hunter, paediatric cardiologist, Professor J Burn, consultant geneticist, Dr E N Hey, Dr A P Kenna, and Dr S W Richmond, consultant paediatricians

The group would particularly like to acknowledge the dedication and drive Mrs M Renwick has shown in coordinating all the information coming into the survey office since the start of the pilot survey in 1984 (and for charming the remaining essential information out of clinicians when it did not reach the survey office spontaneously!) They are also extremely grateful to Miss K Denham at the regional health authority for the skill and flair she showed in handling the computerisation of the complex information generated by this continuing study, the regional medical officer and information services manager for sustained encouragement and support, and OPCS for help with data cross validation.

This report was prepared for the steering group by Dr Hey

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Archives of Disease in Childhood 1992; 67: 775–778

Potential impact of population screening for prenatal diagnosis of congenital heart disease

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Abstract

The potential impact of prenatal screening for the detection of congenital heart disease (CHD) was assessed by prospective analysis of 428 consecutive infant admissions to a supraregional centre; 28 (6·5%) did not have CHD and were excluded from analysis. Of the 400 cases with CDH, 396 (99%) underwent fetal ultrasonography but scanning was performed only before 18 weeks' gestation in 200 (50%). One hundred and forty nine (37%) of all cardiac abnormalities and 149/283 (53%) of severe abnormalities were considered to be detectable prenatally in a screening echocardiographic four chamber view had this technique been used. Prenatal diagnosis of severe CHD actually occurred in only eight (2%) cases and was after 30 weeks' gestation in all. There were 181/347 (52%) of all mothers and 177/253 (70%) of the subgroup with severe abnormalities who expressed an opinion volunteered their preference for termination of pregnancy if mid-trimester diagnosis had been available.

Mid-trimester detection of congenital heart disease rarely occurs at present despite fetal ultrasound scanning in almost all pregnancies. More than half of all severe congenital heart defects seen in infancy are potentially detectable by screening. Major training at primary scan level and modification of the timing of existing fetal anomaly scanning would be required for a screening programme to be effective.

Mid-trimester screening for the detection of fetal anomalies, including congenital heart disease (CHD), is advocated in the UK.[1] Fetal echocardiography is an accurate method for the diagnosis of cardiac defects prenatally.[2] A survey in France demonstrated the feasibility of mid-trimester screening for structural heart disease using a transverse ultrasound section through the fetal thorax to provide a four chamber echocardiographic view of the fetal heart.[3] This has been confirmed in a small number of obstetric units in the UK.[4 5] An increasing number of cases of CHD have been detected prenatally because a heart abnormality was suspected on the routine obstetric scan (fig 1).

This study was undertaken to determine the potential impact on paediatric cardiology practice if a similar antenatal screening programme for CHD was extended to the whole population.

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Accepted 7 February 1992

Methods

British born neonates and infants admitted to the cardiac unit of the Hospital for Sick Children between September 1989 and March 1991 were assessed. A questionnaire was administered (usually by SC, less frequently by IDS) to their mothers within one week of admission. Both parents were present in approximately half of the interviews. Obstetric and birth history, cardiac diagnosis and other congenital abnormalities, acute management, timing of antenatal ultrasound scanning at the local hospital, and the detection of cardiac and extracardiac anomaly prenatally were recorded. Family history of CHD was determined. Parental perception of information offered concerning possible cardiac anomalies at the time of routine prenatal ultrasound scanning at the local hospital was ascertained by asking 'was any comment made about the heart?' In addition, mothers were asked if prior knowledge of a fetal cardiac anomaly would have been helpful, but not specifically about termination of pregnancy.

The normal four chamber view of the fetal heart has characteristic features. The heart occupies about one third of the area of the fetal thorax in transverse section, the two atria are of similar size, the two ventricles are of similar size, and two separate atrioventricular valves meet at the junction of the atrial septum and ventricular septum to form an offset cross (fig 2). For the purposes of this analysis, it was assumed that the four chamber view of the fetal heart would detect fetal

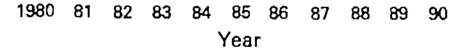

Figure 1 The number of cases of congenital heart defects (CHD) detected annually 1980 to 1990 and the proportion of these referred for assessment because of a suspected abnormality of the fetal heart on the routine ultrasound scan.

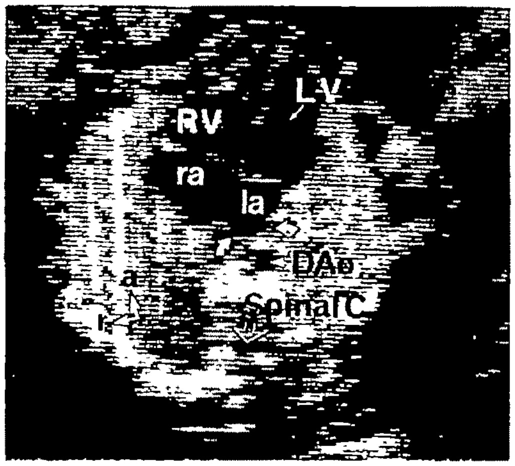

Figure 2 The normal four chamber view of the fetal heart, showing anterior (a), descending aorta (DAo), left atrium (la), left ventricle (LV), right (r), right atrium (ra), right ventricle (RV), and spinal cord (Spinal C)

cardiac anomalies characterised by marked cardiomegaly, obvious disparity between the size of the two atria and/or that of the two ventricles, or major abnormalities of the atrioventricular connection. It was assumed that this single screening view would not detect abnormalities likely to be characterised by less obvious abnormalities of the four chamber view, ventricular septal defects, or even major abnormalities of the arterial pole of the heart such as complete transposition or tetralogy of Fallot.

Cardiac defects were graded arbitrarily as non-severe or severe. Non-severe abnormalities were lesions where either no intervention is likely to be required or where a single surgical or non-surgical intervention with anticipated mortality less than 5% may be necessary. Severe CHD was defined as lesions requiring emergency or elective repair where the perioperative risk nationally was estimated to be greater than 5% and abnormalities which would inevitably require multiple operations to ensure long term survival. Also included in this category were lesions for which survival would depend on palliative surgery or heart transplantation. The necessity for emergency neonatal repair was not, of itself, a determinant of category of severity. Hence, isolated coarctation of the aorta with normal intracardiac anatomy was classified as non-severe whereas coarctation with a large ventricular septal defect was classified as severe.

Spectrum of congenital heart defects

Non-severe (n=117)		*Severe (n=283)*	
VSD	50	Tetralogy of Fallot	54
Coarctation	31	AVSD	53*
PDA	25	TGA±VSD	44
ASD	5	Pulmonary atresia	17
Pulmonary stenosis	3	Pulmonary atresia, IVS	16*
Tricuspid dysplasia	2	HLHS	15*
Pulmonary artery stenoses	1	Coarctation, VSD	11*†
		Aortic interruption	11*
		Tricuspid atresia	8*
		Arterial trunk	8
		Double inlet ventricle	7*
		Critical pulmonary stenosis	7*
		Critical aortic stenosis	2*‡
		Complex TGA/DORV	7*‡
		Ebstein's anomaly	5*
		TAPVC	5
		cTGA, VSD	3*
		Coarctation, LVOTO	3*§
		Aortic stenosis	2
		Aortopulmonary window	2
		Cardiomyopathy	2
		Cardiac tumours	1*

ASD, atrial septal defect, AVSD, atrioventricular septal defect; cTGA, congenitally corrected transposition of the great arteries; DORV, double outlet right ventricle, HLHS, hypoplastic left heart syndrome, IVS, intact ventricular septum,. LVOTO left ventricular outflow tract obstruction, PDA, patent ductus arteriosus, TGA, transposition of the great arteries, TAPVC, total anomalous pulmonary venous connection, VSD. ventricular septal defect

*Detectable on fetal four chamber view

†Includes one patient with aortopulmonary window

‡Lesions with marked ventricular disproportion

§Includes one patient with TAPVC

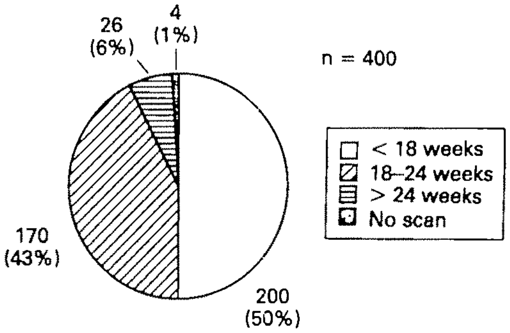

Figure 3 Gestational age at initial fetal ultrasound scan.

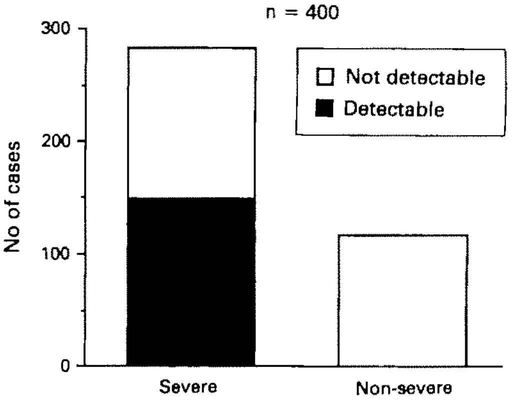

Figure 4 The proportions of non-severe and severe congenital heart defects detectable on a single four chamber screening of the fetal heart.

Results

Twenty eight neonates did not have structural heart disease and were excluded from further analysis. Of the 400 neonates and infants with CHD, 396 had been examined by fetal ultrasound scanning at the local hospital. A single scan had been performed before 18 weeks' gestation in 200 (50%), a further 170 (43%) underwent initial scanning between 18 and 24 weeks' gestation, whereas the initial scans in the remaining 26 (7%) were performed after 24 weeks (fig 3).

The cardiac abnormalities were not severe in 117 (29%) and severe in 283 (71%) cases (table). Of those with severe heart defects, 149 (53%) could have been detected on a screening four chamber view (table, fig 4). In only eight (2%) cases was there a prenatal diagnosis of cardiac anomaly. The diagnosis was made in the third trimester in all of these (fig 5). These eight mothers had been referred for detailed fetal echocardiography because of

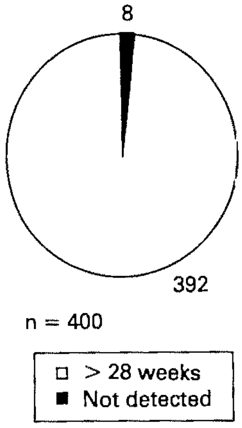

Figure 5 The prenatal detection of congenital heart defects.

suspected cardiac (n=6) or extracardiac (n=2) abnormality on routine antenatal scanning.

There were 193 mothers who believed that they had been reassured about the fetal heart at the time of routine scanning. Among these were 90 cases in whom the cardiac anomaly would have been detectable on a four chamber view. In the remainder no specific reference to the fetal heart had been made. There were 181 (45%) mothers who volunteered their preference for termination of pregnancy had they been aware of the diagnosis, 166 (42%) who indicated that they would have continued the pregnancy even though aware of fetal cardiac anomaly, whereas 53 (13%) did not offer an opinion clearly one way or the other. From the subgroup of 283 mothers of babies with severe congenital heart defects, 177 (62%) would have opted for termination of pregnancy 76 (27%) would have continued the pregnancy, and the choice of the remaining 30 (11%) was not ascertained.

A family history of CHD was present in 10 (2·5%) with a previously affected sibling in six and a parent with CHD in four. Of these 10 infants, four had severe CHD potentially detectable on screening. In addition, 13 babies (all with severe CHD) had an extracardiac anomaly which might have been detected on antenatal ultrasound scanning: diaphragmatic hernia (n=5), hydronephrosis (n=4), omphalocele (n=2), renal cysts (n=1), and absent kidney (n=1). Only six of these extracardiac anomalies were detected prenatally, these led to the prenatal detection of severe CHD after referral for detailed fetal echocardiography in two, both beyond 32 weeks' gestation. Figure 6 shows the potential prenatal detection of cases of severe CHD by population screening, compared with strategies where pregnancies deemed to be at high risk for CHD, because of a family history or because of the detection of non-cardiac anomaly on fetal scanning, are referred for detailed fetal echocardiography. By far the highest proportion of cases is potentially detectable by population screening.

Discussion

THE CASE FOR SCREENING

Advocates of population screening for fetal anomaly have recommended that a detailed fetal anomaly scan be offered at district hospitals at 18 to 20 weeks' gestation.[1] Selected cases might be referred to regional or supraregional centres. In our study group, almost all mothers received fetal ultrasound examination at their local hospital. Prenatal diagnosis of CHD occurred in a tiny minority of this group, and even then was in the third trimester. Most mothers of babies with severe CHD who offered an opinion stated that they would have elected termination of pregnancy if they had been aware of the cardiac anomaly sufficiently early.

The highest yield of positive scans in referral centres is in the group referred with a suspected fetal cardiac abnormality on the four chamber view on the routine scan in the district hospital (fig 1). Obstetric ultrasonographers from one region who were taught to screen the fetal heart detected 69% of heart abnormalities which it was considered could be visualised on the four chamber view.[5] The very low rate of detection of heart abnormalities in our study group was contributed to by prenatal diagnosis and subsequent termination of pregnancy in some cases. Of the 169 cases of CHD diagnosed prenatally in 1990 (fig 1), 23 were from obstetric units in centres which would normally refer infants with suspected CHD to the Hospital for Sick Children. The pregnancy was terminated in 12 of these. It is not appropriate to extrapolate from these numbers directly to the postnatal series because of the different spectrum of abnormalities and high rates of intrauterine death and very early neonatal death in series of heart abnormalities diagnosed prenatally.[2] Nevertheless, it is likely that at least 10 cases of severe severe CHD which would otherwise have appeared in the postnatal group were prevented. The previous strategy in referral centres was to assess in detail designated 'high risk' pregnancies, usually those with a family history of CHD. This approach would not be very rewarding in terms of prenatal diagnosis in new cases in the longer term (fig 6). However, the psychological value afforded to parents with a previously affected child by exclusion of recurrence of severe CHD by detailed fetal echocardiography should not be underestimated.

CHD occurs in 8/1000 live births, about four of which will be severe abnormalities. Our data support the previous suggestion that four chamber screening potentially would detect about two cases of severe CHD per 1000 live births.[2] There are about 700 000 live births annually in the UK.[6] Consequently, an effective national screening programme based on the four chamber view would potentially detect about 1400 cases of severe

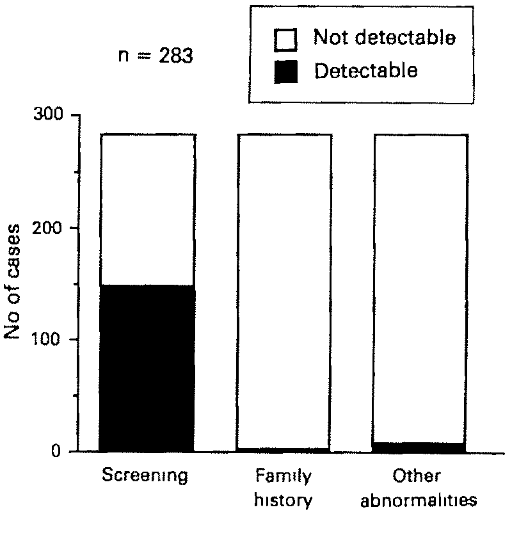

Figure 6 The proportion of cases of severe congenital heart defects detectable by population screening, compared with detailed assessment of the fetal heart in high risk pregnancies (those with a family history of CHD) or those in whom an extracardiac abnormality is detected

CHD annually over and above those cases destined for spontaneous intrauterine or very early neonatal death.

LIMITATIONS

If population fetal anomaly screening is to implemented, current practice and attitudes[7] require modification. The likelihood of detection of fetal cardiac defects is closely related to the timing of scanning and the experience of the ultrasonographer. The ability to image adequately fetal cardiac anatomy on the four chamber view increases rapidly when approaching 18 weeks' gestation. When ultrasonographers are taught to screen the four chamber view, this is obtained in 90% of examinations at 18 weeks' gestation or more, compared with only about 10% of examinations before 18 weeks' gestation.[5] About half of our patients had a solitary routine scan before 18 weeks' gestation. Ideally, routine fetal anomaly scanning would be offered at 18 to 20 weeks' gestation, at a time when adequate visualisation is possible while still providing time for appropriate counselling should an important anomaly be detected. Funding for training programmes for ultrasonographers would be required. There is as yet no estimate of cost, but there would be savings in terms of reduced expenditure in the diagnosis, support, and management of children with serious cardiac defects as many of these parents would elect termination of pregnancy. There has been a marked reduction in the incidence of new patients with hypoplastic left heart syndrome at our supraregional centre over the last three years (45 in 1985–7 compared with 23 in 1988–90) which coincided with an increased rate of prenatal detection.[8] In addition, the increased diagnosis of extracardiac anomalies that would occur with such a programme would almost certainly lead to a postnatal reduction in the incidence of such defects if parents terminate pregnancy in severe cases.

It is feasible to include the four chamber view of the fetal heart in a screening programme for the detection of fetal anomalies. The main drawback is that not all severe CHD will be detected by the four chamber screening view. It is not realistic to include more detailed examination of the fetal heart in a screening programme at present. Our choice of abnormalities which would be detectable on four chamber screening (table) was arbitrary, but intentionally conservative. Experience suggests that ultrasonographers who gain experience of four chamber fetal heart screening are increasingly likely to detect many abnormalities which we categorised as not detectable, including abnormalities of the arterial pole of the fetal heart.

It could be argued that the high proportion of our study group who would have elected termination of pregnancy had CHD been detected sufficiently early in pregnancy is misleading, as the information was obtained often at an emotionally difficult time and without the counselling which is obligatory when fetal anomalies are detected. On the other hand, these parents were experiencing the real consequences of congenital heart defects in their offspring and we were scrupulous not to lead them on this issue. At present, most mothers opt for termination of pregnancy if a severe fetal heart abnormality is detected.[8] The opportunity to consider termination of pregnancy is not the only benefit of prenatal diagnosis, however, and the proportion of parents choosing this option may decrease as surgical results continue to improve. For some lesions, the major continuing mortality may be preoperative,[9] and this is potentially avoidable if prenatal diagnosis occurs. Even neonatal heart transplantation has a higher likelihood of success with prenatal diagnosis as there is a longer time available for donor organ procurement.

CONCLUSIONS

Despite the widespread application of routine fetal ultrasound scanning in local hospitals, only a small percentage of the potentially detectable fetal cardiac defects are currently diagnosed. While the introduction of effective fetal cardiac screening would require major changes to current practice, it is feasible as part of a population based programme of fetal anomaly detection and could be expected to have a major impact on paediatric cardiology practice.

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Archives of Disease in Childhood 1992; 67: 779–783

Cytomegalovirus prevalence in pregnant women: the influence of parity

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Abstract

Over 20 000 women attending for antenatal care at three London hospitals were prospectively studied to determine the prevalence of cytomegalovirus (CMV) antibodies; 54·4% of these women were CMV seropositive. Ethnic group was strongly associated with CMV status: 45·9% of white women were seropositive, 88·2% of Asian, and 77·2% of black women (African/Caribbean ethnic origin). Among 12 159 white women born in the British Isles, seropositivity was independently associated with increasing parity, older age, lower social class, and being single at antenatal booking. The findings are consistent with the hypothesis that, in the UK, child to mother transmission of infection plays a significant part in the acquisition of CMV infection in adult life.

Cytomegalovirus (CMV) is common worldwide and a well recognised cause of handicap in infants born with congenital infection. The majority of congenitally infected infants develop normally, but about 10% are likely to have permanent CMV related damage, ranging from unilateral sensorineural hearing loss to multiple disabilities which can include microcephaly, cerebral palsy, sensorineural hearing loss, impaired vision, and mental retardation.[1]

Congenital infection can follow either primary or recurrent maternal infection, but the likelihood of fetal infection and the risk of associated damage is higher after a primary infection.[2 3] In developing countries, where most people acquire CMV infection in early childhood, most congenital infections follow maternal recurrent infection. In the UK, although acquisition of CMV infection in infancy is common (largely attributable to transmission from seropositive mothers at delivery or through breast feeding[4]), more than 60% of women reach adult life still susceptible to CMV and about three quarters of congenital infections are likely to be attributable to primary maternal infection.[5]

Sexual transmission is acknowledged to play an important part in the acquisition of CMV infection in adult life.[6 7] Studies in the USA examining the transmission of CMV in day nurseries have suggested that children may also be an important source of infection for their mothers or other caretakers.[8 9] The relative importance of contact with children in comparison with other modes of transmission of infection in adult life is unclear and will depend on a number of factors relating to breastfeeding, sexual and child rearing practices, which vary considerably between countries and social and ethnic groups. The relative importance of different modes of transmission of CMV in the UK is unknown, although there is some anxiety about the possibility of occupational risk for women working with young children.[10]

The present analysis is based on data collected as part of a large prospective study of CMV infection in pregnancy carried out in west London between 1980 and 1986. The main aims of the study were to examine the CMV serological status of women booking for antenatal care, estimate the incidence of congenital CMV infection, and investigate its long term sequelae.[3] This paper explores the independent effects of social class, marital status, age, and parity on maternal seroprevalence at antenatal booking.

Subjects and methods

All women booking for antenatal care at three west London hospitals were eligible for enrolment in the study, which continued for one year at the first hospital, two years at the second, and six and a half years at the third. Details of maternal age, parity, marital status, country of birth, race, and both maternal and paternal occupation were collected by interview at the first antenatal appointment, together with a blood sample to establish CMV serological status. Sera were tested for CMV antibodies by complement fixation, and detection of specific antibody at a dilution of 1:10 was taken to indicate past CMV infection. While this assay may be less sensitive than others now available, it is acceptable for epidemiological purposes; any slight inaccuracy in the overall estimation of seroprevalence will not affect the internal comparison of results presented here.

Analysis of the whole dataset was carried out using SAS.[11] A grouped binomial relative risk regression[12] was performed on a subset of the data, white women born in the British Isles, to explore the independent roles of parity, marital status, social class, and age.

Women were assigned to five parity groups, ranging from those who had no previous children to those who had four or more. Two marital status groups were defined: one comprising women who were married or cohabiting at the time they booked for antenatal care, and the second those who were single, divorced, widowed, or separated (hereafter referred to as

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Accepted 7 January 1992

single). Social class was categorised by partner's occupation for married and cohabiting women, and by their own occupation for single women,[13] and was then divided into four occupational groups: professional (Registrar General's social class I and II), clerical (III non-manual), manual (III manual, IV, and V), and unclassified (unemployed, students, housewives, and armed forces). Finally, the mean age of each subgroup of women was calculated and used as the age value of that subgroup in the regression.

Results

Altogether 21 382 women who booked consecutively for antenatal care were enrolled into the study. Many of these women booked for more than one pregnancy during the study period, but only the first pregnancy in which a blood sample was collected was included in this analysis; the CMV serological status of 20 684 women (94·5%) was known.

The overall CMV seroprevalence was 54·4%, but the study population was ethnically diverse and ethnic group was strongly associated with seroprevalence, Asian women having the highest level, 88·2%, and white women the lowest, 45·9% (table 1). There were marked differences in both seroprevalence and demographic characteristics between women of the same ethnic group who were born in different countries. In addition, British born women of all ethnic groups were less likely to be seropositive than those born elsewhere, and also tended to be younger and more often single. It is likely that family structure and organisation, and arrangements for the care of young children, also varied between the different groups.

The complex relationship of age, parity, social class, marital status, and CMV seroprevalence was therefore explored in the homogeneous subgroup of this London population, the 12 559 white women born in the British Isles. The overall CMV seroprevalence in this subgroup was 42·8%. As shown in table 2, there was a clear trend of rising seroprevalence with increasing age from 36·6% in those under 20 years to 51·4% in women aged 35 and over, and with increasing parity from 38·9% in nulliparous women to 66·2% in women expecting their fifth or subsequent child. Single women were more likely to be seropositive than those with a partner, and the lower the social class the higher the proportion of seropositive women.

The figure shows the CMV seroprevalence by age and parity. While there was a steady and gradual rise in seropositivity with age for nulliparous women, this was not the case for parous women. The more children a woman already had, the higher the probability of being seropositive, and the smaller the effect of increasing age. Indeed, younger women of high parity were more likely to be seropositive than older women. This suggests that there is a particularly high rate of acquisition of CMV infection in young parous women.

Table 1 Ethnic group and CMV seroprevalence

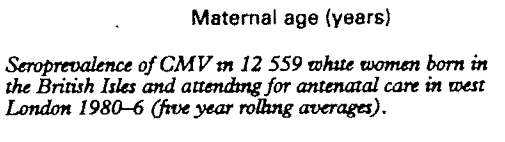
Ethnic group (No in group)	*Seroprevalence (%)*	*95% Confidence interval (%)*
Asian (1939)	88 2	86·8 to 89 7
Black (1972)	77·2	75·3 to 79 0
Oriental (533)	83·9	80 7 to 87 0
White (15 585)	45·9	45·1 to 46 7
Other (157)	58·0	50·2 to 65·7
All women (20 684)	54·4	53 6 to 55·0

Table 2 CMV seroprevalence and age group, parity, marital status, and social class in 12 559 white women born in the British Isles

	Seropositive (%)	*95% Confidence interval (%)*
Overall	42·8	41·9 to 43·7
Age group (years):		
<20	36 6	33 6 to 39·7
20–24	39·8	37·9 to 41·7
25–29	41·7	40·2 to 43·2
30–34	44·5	42·8 to 46 0
35+	51 4	48·8 to 54·1
Parity group:		
0	38·9	37 8 to 40·0
1	46·4	44 7 to 48 1
2	49·5	46·7 to 52 4
3	55·4	50·3 to 60·5
4+	66 2	58·9 to 73·6
Marital status:		
Single	46·9	44·8 to 49·0
Married/cohabiting	41·9	40·9 to 42·9
Social class.		
Professional	40·0	38·7 to 41·4
Clerical	43 5	41·3 to 45 6
Manual	45·2	43 6 to 46·9
Unclassified	45·5	43·1 to 47·9

To estimate the independent effects and thus the relative importance of age, parity, marital status, and social class, a binomial relative risk regression was carried out on the 12 159 (96·8%) members of the subgroup for whom all the variables of interest were available.

Two models were fitted: in the first, all four variables were categorical; and in the second, social class and marital status were categorical, and age and parity continuous. The first model accounted for slightly more of the variance than the second, but the difference between the two was not significant at the 5% level; the second model was therefore used so that age and parity effects could be estimated per year of age and per previous child born. The possibility that there might be interaction between the factors was explored. The only statistically significant interaction was that between age and parity, with parity having a greater effect on seroprevalence in younger



Seroprevalence of CMV in 12 559 white women born in the British Isles and attending for antenatal care in west London 1980–6 (five year rolling averages).

Table 3 Logistic regression for 12 159 white women born in the British Isles, showing log likelihood χ^2 tests and estimated relative risks

	χ^2	*df*	*Relative risk*	*95% Confidence interval*
Age (per 5 years)	68·1*	1	1·117	1·09 to 1·15
Parity (per baby)	70·9*	1	1·140	1·11 to 1·18
Social class	35·3*	3		
Professional			1	
Clerical			1·102	1·04 to 1·17
Manual			1·166	1·11 to 1·23
Unclassified			1·128	1·05 to 1·21
Marital status:	45·9*	1		
Married/cohabiting			1	
Single			1·233	1·17 to 1·30
Age (per 5 years, per baby)	9·3**	1	0·973	0·96 to 0·99

Baseline CMV seroprevalence 33·05% (95% confidence interval 31·6% to 34·5%) (nulliparous, age 25, married, professional social class).
*Extra deviance to remove from model with main effects only.
**Extra deviance to add to main effects model

women than in older women; this term was therefore added to the model.

Table 3 shows the χ^2 value, relative risk for seropositivity for each factor, and its 95% confidence interval; the χ^2 value tests the statistical significance of each factor when the others are held constant. Age and parity were most strongly associated with seroprevalence, followed by marital status, and then social class.

The risk of being seropositive increases with each successive child. A 25 year old woman having her second child is an estimated 1·14 times more likely than a nulliparous woman of the same age to be seropositive, if she is having a third child this increases to 1·3 ($1{\cdot}14^2$) and for her fourth to 1·48 ($1{\cdot}14^3$). Because of the negative interaction between age and parity, the increased risk associated with higher parity is less in older women. For a woman aged 35, the corresponding figures relative to a nulliparous woman aged 35 are 1·08, 1·16 and 1·26 (for instance the latter is $1{\cdot}14^3 \times (0{\cdot}973^2)^3$).

This can be compared with the relative risks for the other factors: a 30 year old nulliparous woman is estimated to be 1·12 times more likely to be seropositive than a 25 year old nulliparous woman of the same marital status and social class; a woman who works (or whose partner works) in a manual occupation is 1·17 times more likely than a professional woman to be seropositive; a single woman is 1·23 times more likely than a married or cohabiting woman to be seropositive. The relative risks combine multiplicatively, so a single 25 year old woman with one child is 1·41 ($1{\cdot}14 \times 1{\cdot}233$) times more likely than a nulliparous married 25 year old of the same social class to be seropositive.

Discussion

The epidemiology of CMV in a particular population, and the relative importance of different modes of transmission, are likely to be determined by cultural practices relating to breast feeding,[4 14] child rearing, child care arrangements,[15] and sexual behaviour.[6 16–18]

Ethnic group was an important determinant of CMV seroprevalence in this London population. Women who were born in countries where CMV seroprevalence is high at young ages (for instance, parts of Africa,[19] South America,[20] Asia,[21] and southern Europe[22 23]) had rates of seroprevalence which probably reflected their acquisition of infection in infancy and childhood. Similar observations have been made in other studies carried out among ethnically diverse populations.[24–27]

In order to explore the independent effects of social class, marital status, age, and parity, a restricted analysis was undertaken of the factors associated with seropositivity in a homogeneous subgroup with a high proportion of women susceptible to primary CMV infection during their childbearing years: approximately 12 500 white British born women. Each of the four factors, parity, age, social class, and marital status, had a strong independent association with CMV seroprevalence.

The independent association of parity with seroprevalence, having controlled for the other factors, was particularly striking. In all age groups women of higher parity were more likely to be seropositive than those having their first or second child.

This effect of parity among women of the same age could be accounted for by child to mother transmission of infection, from children who had themselves acquired infection from elsewhere. A number of nursery studies have documented child to child transmission of infection, and examples of children and nursery staff sharing the same virus strain have been identified.[28–30] Studies in the USA have found high rates of seroconversion among some day care workers,[31–33] and children who acquire infection in day nurseries have been shown to transmit infection to their susceptible mothers,[15] as have infants who were infected through blood transfusion.[8]

Several other studies have observed an association between parity and CMV status. A longitudinal study in a middle class population in Houston, USA,[34] found that the presence of young children in the home was a risk factor for primary infection in pregnancy, and that maternal seropositivity was associated with the presence of older children.[26] The Alabama group also observed a rising seroconversion rate with subsequent pregnancies in a high socioeconomic group.[35]

An alternative, or additional, explanation for the association of parity and seroprevalence could be that women who have had more pregnancies have also, on average, had more previous sexual partners. In an evaluation of the relationship between sexual practices and CMV seroprevalence among women in Seattle, USA,[7] sexual activity was an important determinant of seropositivity, but the association was stronger for white than for black women, and in addition, parity was associated with seropositivity in the white but not in the black women.

Much of the crude effect of age on seroprevalence was accounted for by parity, but even after controlling for the other factors a major independent age effect remained. A relatively high incidence of primary infection in infancy is probably followed by a lower incidence through childhood, which increases in adolescence with the onset of sexual activity.

Tempting though it is to attribute the rise in seropositivity with increasing age to the acquisition of infection in adult life, this interpretation of cross sectional age specific seroprevalence data could be misleading. Different birth cohorts of women may have experienced different rates of acquisition of infection in infancy, adolescence, and adult life as a result of changing patterns of breast feeding and sexual activity

Infants born to seropositive women may acquire CMV infection during delivery,[36 37] or through breast feeding;[14] currently approximately 20% of children born in Britain are likely to be seropositive by the age of 12 months.[4] Virtually all women enrolled in this study were born between 1935 and 1970, a period which saw an appreciable decline in breast feeding. Until the 1930s most children were breast fed for several months, but by 1946 only 45% of British babies were still breast fed at the age of 2 months,[38] and by 1970 this had declined to only 30% at the end of the first week.[39] CMV is more likely to be present in breast milk after the first week than before, and colostrum is a relatively poor source of virus.[4 40] It is therefore likely that some of the apparent effect of increasing age in this population is related to lower levels of CMV infection in infancy in the younger women.

Age at first sexual intercourse, number of sexual partners, and the use of barrier methods of contraception have all been associated with CMV seroprevalence,[7] and are also factors which are likely to show both a cohort effect and social class differences.

This analysis demonstrated an interaction between parity and age, in that the association of high parity with seropositivity was greater in younger women than in those who were older. Indeed, women who were pregnant with a fifth child by their mid to late 20s were more likely to be seropositive than older women of high parity, who had presumably either spaced their children out more, or started having them later.

Several studies have shown an association between seroprevalence and social class,[35 41] and some studies of seroconversion in pregnancy have been restricted to higher socioeconomic groups in order to enrol a relatively high proportion of seronegative women. It is possible that single pregnant women have had, on average, a greater number of sexual partners than married or cohabiting pregnant women, and this could, to some extent, account for the association of single status with seropositivity. However, seroprevalence may be associated with child care arrangements, as discussed above, and use of day care is strongly influenced by both social class and marital status, as well as maternal age and most obviously parity. In most of the UK, and certainly in the London area from which the study population was drawn, access to day care facilities is highly dependent on family situation and socioeconomic status. Women of low socioeconomic status are more likely than professional women to have their children cared for in day nurseries; single women and very young women, particularly those who have several children, are also more likely to use these facilities.

Conclusion

Within each age band and social class group, women with children are likely to differ from those without children, and it is difficult, using cross sectional data, to disentangle the effects of social and cohort factors, such as child care arrangements, breast feeding experience, and sexual history. None the less, in this study the independent effect of parity, having allowed for age, social class, and marital status, was very striking and certainly consistent with the hypothesis that children are an important source of infection for their susceptible mothers.

We thank the medical, nursing, and clerical staff and the women attending for antenatal care at Charing Cross (West London Hospital), Central Middlesex, and Queen Charlotte's Hospitals during the study period, and also the laboratory staff, in particular Mr Kong Shin Chin. We also thank Dr Stuart Logan for his helpful comments.

This work was supported by grants from the National Fund for Research into Crippling Diseases, the Medical Research Council, and the Child Health Research Appeal Trust.

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Archives of Disease in Childhood 1992, 67: 784–788

Skin temperature and heart rate rhythms in infants of extreme prematurity

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Accepted 18 February 1992

Abstract

Nine preterm infants of 26 to 29 weeks' gestational age and 792 to 1200 g birth weight spent six to 17 weeks in our neonatal medical unit. Hourly recordings of skin temperature and heart rate were carried out. The first five to 15 weeks were spent in the intensive care ward, in continuous light, due to various medical conditions. After recovery they were moved to a nursery for one to nine weeks, with 12 hourly periods of light and darkness. Four infants developed circadian rhythms in temperature and three in heart rate in light-dark periods, the remainder failing to do so. Some infants take longer than others to develop circadian rhythms but the reasons for this are not clear. It is suggested that earlier exposure to a light-dark environment may synchronise the 'body clock' to a 24 hour period in more preterm infants.

In human fetuses circadian rhythms have been reported in heart rate, breathing movements, and motility.[1 2] There is some uncertainty, however, about whether such rhythms are imposed by the maternal environment or are due to the development of the fetal nervous system including the 'body clock'. A weak effect only from the body clock is inferred from the observation that the suprachiasmatic nuclei (the presumed site of the body clock in adults) are poorly developed histologically,[3] and that neonates have poorly developed circadian rhythms.[4] The direct imposition of rhythmicity on the fetus from the maternal environment is suggested by the observation that maternal and fetal rhythms appear to be phase locked.[1 2]

Two recent studies suggest a role for external rhythmicity in preterm infants nursed in intensive care units.[4 5] First, preterm infants appear to benefit from exposure to alternating periods of light and darkness in an intensive care unit.[5] Subsequent to leaving hospital they slept for longer periods and spent less time feeding but showed better weight gain than a control group exposed to continuous lighting after they had received intensive care. Second, in preterm infants nursed in an enviroment with day or night time cues comparable with those in term infants, circadian sleep-wake rhythms were observed at an earlier postconceptional age in those born preterm.[4]

In our neonatal medical unit we have investigated the development of rhythmic changes in heart rate and skin temperature in infants of extreme prematurity who had been with us for prolonged periods. In particular, we have investigated if the imposition of a rhythm of light and darkness produces a direct effect upon the infants with higher heart rates and skin temperatures in the light phase and lower values in the dark as occurs in infants who are diurnally active and sleep at night.[5] In this observational study we deliberately chose not to manipulate the light-dark environment in which the infants were nursed. Instead, we wished to examine the extent to which circadian rhythms develop naturally among very preterm infants who had prolonged neonatal illnesses requiring intensive care, and who, after recovery, were transferred to a special care nursery where it was the policy to dim the lighting during the night.

Subjects and methods

INFANTS

Nine preterm infants of 26 to 29 weeks' gestational age born between January 1989 and December 1990 had spent six to 17 weeks in our neonatal medical unit (table 1). These were the infants who had continuous measurements (at one hourly intervals) of heart rate and skin temperature for a prolonged period covering the time they were nursed in continuous light-light and subsequently in a light-dark environment. Initially all were admitted to the intensive care ward and nursed in incubators. Continuous recordings of skin temperature and heart rate were carried out using skin electrodes which were attached to a monitor (Hewlett-Packard). For skin temperature measurement the electrode was applied to the anterior abdominal wall. The heart rate and electrocardiogram were obtained simultaneously from electrocardiogram skin electrodes applied to the right and left chest wall and the right lower limb. The nursing staff entered the heart rate and skin temperature at hourly intervals on charts and data from these charts were used in the analysis. Medical and nursing care were provided as required including ventilatory support, phototherapy, antibiotics, and infusions of solutions containing electrolytes, glucose, and lipids for nutrition. Arterial, venous, or capillary blood samples were taken when indicated for clinical investigations. Parents visited their infants and handled them whenever possible. Nasogastric tube feeds at one hourly intervals were started when the infant's condition had improved. Ward lighting (of the order of 1300 lux) was continuous during this period. The duration each infant spent on this ward is shown in table 1.

After recovery from their acute medical conditions the infants were transferred to an

Table 1 Details of infants studied

	Case No								
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
Delivery	Breech, vaginal	Cephalic, vaginal	Cephalic, vaginal	Cephalic, vaginal	Cephalic, vaginal	Cephalic, vaginal	Cephalic, vaginal	Caesarean section	Cephalic, vaginal
Apgar scores									
1 min	3	7	6	6	2	2	6	6	3
5 min	3	9	3	8	2	2	8	8	9
Gestational age (weeks)	26	26	26	26	27	28	28	29	28
Birth weight (g)	1032	957	800	792	800	1200	1100	1001	957
Neonatal conditions.									
IRDS	+	+	+	+	+	+	+	+	
Pneumonia		+					+		
Pneumothorax	+				+	+		+	
Jaundice	+	+	+	+		+		+	+
Sepsis	+	+	+	+	+	+	+	+	+
IVH only								+	
IVH with dilated ventricles	+		+			+	+		
IVH with parenchymal extension			+						
IVH with periventricular cysts (leucomalacia)		+							
Retinopathy	+	+	+		+				
Chronic lung disease	+	+	+	+		+	+	+	
Preterm bone disease			+	+					
Patent ductus arteriosus			+						+
Duration in intensive care ward (weeks)	9	13	6	9	15	13	9	5	5
Duration in nursery (weeks)	8	4	9	2	2	1	1	2	1

IRDS=idiopathic respiratory disease, IVH=intraventricular haemorrhage.
+=Condition present

adjacent nursery where they spent a variable amount of time (table 1). They were fed at intervals of two, three, or four hours with milk by a nasogastric tube, as larger milk volumes were accepted (200–250 ml/kg/day); bottle feeds were offered subsequently. Visiting by parents was continued. While in the nursery the infants were nursed in a light-dark environment—that is, the light was dimed (20 lux) during the night (2000–0800 hours) and visitors and staff were urged to make less noise. For the rest of the time, the light was maintained at a higher level (180 to 300 lux) and there was also a higher level of general activity in the nursery.

ANALYSIS OF DATA

An effect of the light-dark cycle either direct or through synchronisation of the body clock would produce significantly higher mean heart rates and skin temperatures during the light as compared with the dark phase. We have, therefore, compared the skin temperature and heart rate values obtained in the last week in light-light with those obtained during the one or more weeks that each baby spent in light-dark. For statistical purposes, we have proceeded as follows.

For each day that a baby spent in light-dark we have calculated the mean value obtained in the light (hourly values from 0900–2000 hours) and the mean value in the dark (hourly values from midnight to 0800 and 2100–2300 hours). Dividing the results into weekly blocks then enabled us to compare the seven mean light and dark values (Student's paired *t* test, df=6). For comparison we have used the seven last days spent in light–light, calculating for each day the mean of the values obtained between 0900 and 2000 hours and the mean of the 12 values at the other times, and then comparing these seven means, again by paired *t* tests. For illustrative purposes we have divided the results into weekly blocks to calculate for each hour the mean value from the seven days.

Results

The statistical summary is given in table 2.

For skin temperature, the only significant difference between 'daytime' (0900–2000 hours) and 'night time') values in the last week in light–light was in case 2 where the night time values were ***higher***. When placed in the light–dark environment three babies showed some response during the first week (cases 6, 8, 9), five babies showed no response (cases 1, 3, 4, 5, 7), and case 2 showed a delayed response. This last baby is particularly remarkable as the rhythm was initially inverted (daytime values lower than night time), as in light–light, and became phased as predicted (daytime values higher) only by week 3 in light–dark. Examples of this 'delayed responder' (fig 1), 'immediate responders' (figs 2, 3) and 'non-responder' (fig 4) are illustrated for cases 2, 9, 6, and 5 respectively.

For heart rate, three babies showed night time values higher than daytime in the last week in light–light (cases 2, 3, and 8). In light–dark again there were non-responders (cases 1, 3, 4, 7, 8, and 9), an immediate responder (case 6), and delayed responders (case 2 and 5). Figure 5 illustrates the immediate response of case 6.

Table 2 Mean difference (n=7 days) between average of 0900–2000 values and 2100–0800 values in heart rate and skin temperature

Case No		Skin temperature				Heart rate				First light–dark (weeks)	
		Last light–light	Light–dark			Last light–light	Light–dark			Postnatal age	Postconceptional age
			1	2	3		1	2	3		
1	Mean	−0·139	−0·183	+0·080	−0·139	+1·129	+0·114	+0·171	+0·529		
	SE	0·078	0·109	0·108	0·064	2·913	3·164	2·365	2·580	10	36
	p Value										
2	Mean	−0·261	−0·210	−0·081	+0·129	−6·528	−3·786	−1·614	+4·543		
	SE	0·132	0·089	0·075	0·057	3·357	1·661	1·064	1·328	14	40
	p Value	*	*		*	*	*		†*		
3	Mean	−0·077	−0·099	−0·170	+0·103	−3·986	−4·271	−2·457	−4·857		
	SE	0·100	0·078	0·093	0·093	1·841	2·655	1·969	0·848	7	33
	p Value					*			†*		
4	Mean	+0·033	−0·120	−0·144		−0·486	−5·743	+2·300			
	SE	0·072	0·070	0·098		2·324	2·591	2·244		10	36
	p Value						*				
5	Mean	+0·123	+0·047	+0·050		+4·929	+1·000	+5·514			
	SE	0·208	0·133	0·070		3·891	1·890	2·081		16	43
	p Value							†*			
6	Mean	+0·041	+0·497			+0·357	+7·943				
	SE	0·106	0·100			1·524	2·276			14	42
	p Value		†*				†*				
7	Mean	−0·003	+0·100			−0·900	+1·400				
	SE	0·088	0·145			1·622	2·933			10	38
	p Value										
8	Mean	+0·080	+0·139	−0·131		−5·443	−0·943	−2·214			
	SE	0·082	0·060	0·093		1·977	3·240	1·398		6	35
	p Value		*			†*					
9	Mean	−0·020	+0·266			+1·429	+2·743				
	SE	0·160	0·069			3·164	1·995			6	34
	p Value		†*								

p<0·05, †=p<0·02

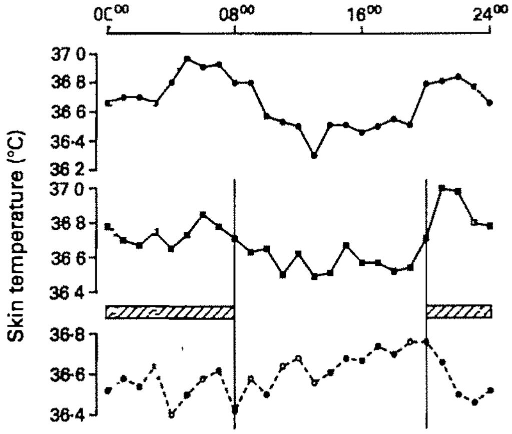

Figure 1 Mean hourly values of skin temperature in case 2 during the last week of light–light (●, upper), first week of light–dark (■, middle), or third week of light–dark (○, lower). Shaded area indicates when lights dimmed during weeks of light–dark, vertical lines separate light and dark phases.

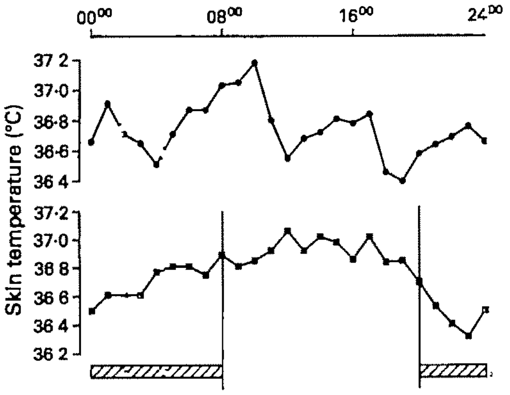

Figure 2 Mean hourly values of skin temperature in case 9 during the last week of light–light (●) or first week of light–dark (■). Shaded area indicates when lights dimmed during weeks of light–dark, vertical lines separate light and dark phases.

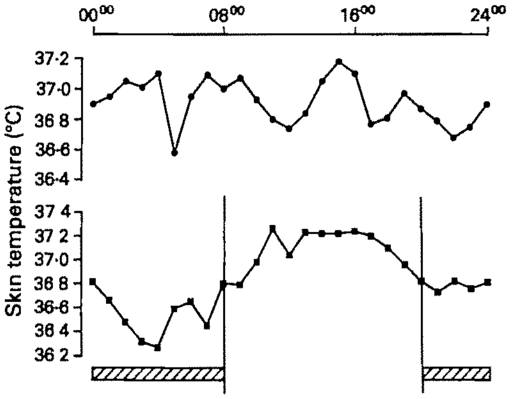

Figure 3 Mean hourly values of skin temperature in case 6 during the last week of light–light (●) or first week of light–dark (■). Shaded area indicates when lights dimmed during weeks of light–dark, vertical lines separate light and dark phases.

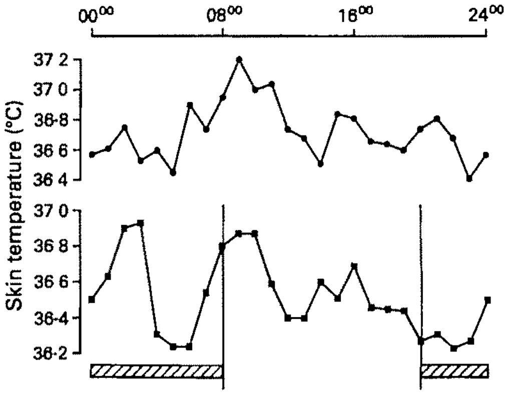

Figure 4 Mean hourly values of skin temperature in case 5 during the last week of light–light (●) or first week of light–dark (■). Shaded area indicates when lights dimmed during weeks of light–dark, vertical lines separate light and dark phases

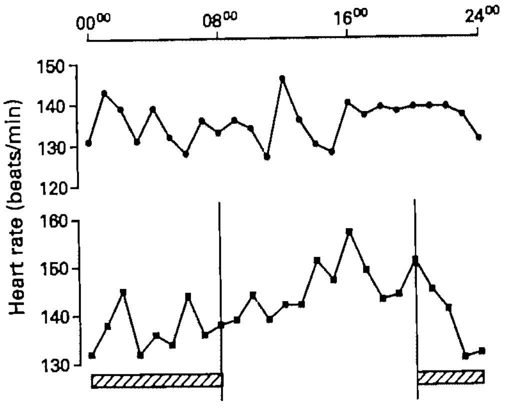

Figure 5 Mean hourly values of heart rate in case 6 during the last week of light–light (●) or first week of light–dark (■). Shaded area indicates when lights dimmed during weeks of light–dark, vertical lines separate light and dark phases.

The effect, or lack of it, upon heart rate of placing the babies in the light–dark environment was similar to that upon skin temperature in most cases, but different in babies 5, 8, and 9 as regards statistical significance.

The infants who had developed circadian rhythms did not seem to differ systematically from those who had not with respect to mode of delivery, Apgar scores, gestational age, birth weight, neonatal conditions, duration spent in the intensive care ward or postconceptional age (table 1). The extent to which a neurological insult will delay the development and entrainment of circadian rhythms is not clear. It is worthy of note that three of four infants who developed circadian rhythms in skin temperature and heart rate in a light–dark environment had a history of periventricular cysts (leucomalacia) or an intraventricular haemorrhage (cases 2, 6, 8; table 1). In the remaining five infants who did not develop circadian rhythms (non-responders) three had a history of intraventricular haemorrhage with dilated ventricles (cases 1, 3, 7). As these infants were not studied after leaving hospital it is not possible to say how long it took the non-responders to develop circadian rhythms.

Discussion

In preterm infants of less than 30 weeks' gestational age the postnatal onset of circadian rhythms in heart rate and skin temperature has shown considerable variability. In a third of our infants circadian rhythms were observed in the first week or so in light–dark while in the remaining two thirds none was detected during this time span. In a previous study Mirmiran *et al* investigated nine infants of 26 to 32 weeks' gestational age in whom circadian rhythms of rectal temperature were reported in five infants at postconceptional ages of 28 to 34 weeks, during a one to three day period of nursing in a light–dark environment.[6] Their group of infants were unusual in having remarkably few neonatal medical conditions which are known to occur in infants of extreme prematurity, including those mentioned in table 1. This raises the possibility that such medical conditions may have contributed to the delayed onset of circadian rhythms in our infants.

We defined appropriately phased circadian rhythms in skin temperatures and heart rates in our infants as those in which the mean values of the measurements carried out were significantly higher in light than in darkness. This is in keeping with observations which are well known in adults.[7] Mirmiran *et al* in their study reported circadian rhythms but with maximal rectal temperatures in periods of darkness rather than in light as was found for heart rate for case 3 in our study.[6] Another of our infants (case 2) showed a similar rhythm but for a transient period only while the infant was in light–light and the first two weeks in a light–dark environment. We suggest that this might represent a 'free running' rhythm that occurs in some infants until light–dark cycles or social cues from feeding or handling them act as external time cues (zeitgebers) to synchronise the endogenous pacemaker (body clock) to a 24 hour period.[7]

The earliest observation of an appropriately phased circadian rhythm in heart rate or skin temperature in our infants, suggesting that the body clock was synchronised, was at a postconceptional age of 34 weeks. By contrast diurnal variations in fetal heart rate have been reported as early as 20 to 22 weeks' gestation.[2] It may be that the fetus is affected by maternal influences (hormonal, temperature, or blood supply).[2] A direct effect of light–dark cycles in utero is unlikely and even full term infants do not always respond to a similar influence shortly after birth.[4] In our infants exposure to light–dark cycles took place after recovery from their medical conditions when they may have been more active in the daytime, the staff and parents would handle them more frequently and noise levels tended to be higher in the nursery. These associated events provide further environmental cues which may contribute to the development of circadian rhythms in light–dark periods.[7] The tendency for rhythms in skin temperature and heart rate to develop at a similar age, observed here and in other studies,[7] would be predicted as they both change with behavioural responses to the environment.

It has been suggested that a single caregiver (the mother) may convey circadian information to a newborn infant by either her pattern of behaviour or feeding routine.[4] In our nursery each infant would have been handled by various nurses and doctors when fed, given a bath or medically examined. In addition, they would have been handled by parents during a visit. By contrast while at home the mother would have had an overall role in handling the infant. However, it is not clear to what extent infants can perceive or recognise those who handle them. If it is thought that the development of circadian rhythmicity, and its entrainment, is to some extent related to increased sensory input then there would be an argument for increasing diurnal handling of infants in a nursery.

In neonatal intensive care units survival rates of very low birthweight infants have improved in recent years, including those of less than 30 weeks' gestational age who appear to approach the edge of viability. As such infants usually remain in hospital for prolonged periods an optimal environment for neonatal intensive care that includes exposure to periods of light and darkness may lead to subsequent benefits in sleeping pattern and weight gain.[5] If the fetus were not born prematurely it would continue in a rhythmic environment in utero. After preterm birth nursing infants in a rhythmic environment may therefore have important implications for subsequent development.[5] Our findings suggest that for such infants the duration spent in the nursery in light–dark periods appears to be important for the entrainment of circadian rhythms. Hence, some consideration should be given for the earlier introduction of light–dark periods as the preterm infant like the developing fetus may be influenced by a rhythmic environment.[2 5] The appropriate time for doing this after the infant's condition has stabilised in the intensive care ward and the importance of light intensity which varies between ours and previous studies require further investigation.[4–6]

Observational studies, such as this, provide a range of uncontrolled factors such as varying duration of exposure to continuous lighting before nursing in a light–dark environment, and different illnesses in a group of extremely preterm babies of different gestational ages. These are precisely the circumstances which commonly occur in busy neonatal units. Our results show that, given these usual circumstances, some but not all infants are capable of developing circadian rhythms relatively early (within three weeks) of exposure to a light–dark environment.

These results provide some ethical justification for further studies of the effect of manipulating the light environment of extremely preterm babies during intensive care to assess whether circadian rhythms can be induced earlier.

The help received from the nursing staff in the Neonatal Medical Unit is gratefully acknowledged.

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Archives of Disease in Childhood 1992; 67: 789–792

Prediction of impaired metabolic adaptation by antenatal Doppler studies in small for gestational age fetuses

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Accepted 9 March 1992

Abstract

The increased risk of hypoglycaemia for infants who are small for gestational age (SGA) is well known, and further information regarding metabolic adaptation can be gained by examining the profiles of glucose and other metabolic fuels in such infants. Not all SGA infants experience hypoglycaemia, however, and the ability to identify, antenatally, those at most risk would be helpful for obstetric and neonatal management. This study investigated metabolic differences between two groups of SGA infants who had antenatal umbilical artery Doppler studies. Fourteen had end diastolic velocities (EDV) present and 11 had absent EDV.

The absent EDV group had significantly lower non-esterified fatty acid (NEFA) concentrations at birth, and lower blood glucose and NEFA concentrations in the first six hours after birth. After the first day, few metabolic differences were found between the two groups.

Antenatal Doppler studies may identify those SGA infants who fail to achieve neonatal metabolic adaptation and are most at risk of early neonatal hypoglycaemia.

The healthy fetus receives a constant supply of nutrients from its mother via the placental circulation. Even at times of maternal fasting, fetal blood glucose concentrations are usually maintained as a result of metabolic changes in the fetus itself. After birth, the healthy neonate responds to the cessation of intrauterine nutrition by mobilising glycogen stores to produce glucose, and by initiating gluconeogenesis from amino acids and other substrates. Lipolysis and β-oxidation of fatty acids provide alternative fuels to glucose and the energy necessary for gluconeogenesis.

It is well known that infants who are small for gestational age (SGA) are less able to achieve the metabolic adaptation required of them at birth and are at risk of hypoglycaemia[1 2] and, in some cases, hyperglycaemia.[3] We also have found differences between SGA and normal infants in terms of ketone body production and the ability to utilise gluconeogenic precursors in the early neonatal period.[4] The clinical implications of such reduced availability of metabolic fuels are not yet clear, but recent studies have suggested that neonatal blood glucose concentrations below 2·6 mmol/l are associated with adverse neurological effects, especially for preterm infants.[5 6]

Some metabolic effects of being SGA may be evident antenatally, such as hypoxia, acidosis, hyperlactataemia, and hypoglycaemia.[7 8]

However, not all SGA infants experience failure of metabolic adaptation and it would be of obstetric, paediatric, and maternal benefit to identify those fetuses most at risk. Male SGA infants in particular are thought to be most at risk of neonatal hypoglycaemia,[9] and it appears that the size and relative body proportions of the infant affect vulnerability.[9 10] Doppler ultrasound studies of the umbilical vessels have suggested that this antenatal test can identify SGA fetuses at risk of significant morbidity and mortality.[11]

The purpose of the present study was to compare the metabolic changes seen after birth in a group of SGA infants for whom end diastolic velocities were present on antenatal Doppler study, and a group of equally SGA infants for whom end diastolic velocities (EDV) were absent, to investigate whether abnormal Doppler studies predicted failure of metabolic adaptation. If this hypothesis were true, Doppler studies would then add information to that available from fetal measurements, and might influence clinical management of such small fetuses.

Subjects and methods

Twenty five normally formed singleton infants of mixed gestational age, identified by antenatal ultrasound assessment of fetal weight as being SGA, and who subsequently had birth weights that were more than two standard deviations below the mean for gestational age, were studied. Fetal umbilical Doppler ultrasound studies were carried out using continuous wave Doppler ultrasound (Doptek) with a 100 Hz filter. Waveforms typical of the fetal umbilical artery were identified and included continuous flow consistent with umbilical venous flow in the opposing channel. The umbilical artery was examined at three different anatomical areas. In all cases, the pulsatility index (A-B/mean) was calculated for at least five cycles and the results from the three areas averaged. The last examination carried out within five days of delivery was used to classify the fetus. The result was considered abnormal when EDV were absent (11 fetuses), and normal when EDV were present (14 fetuses).

Umbilical venous blood was taken at delivery and infants were sampled before their first feed or institution of intravenous glucose infusion. Intravenous and enteral fluids were given according to nursery protocols; in order to standardise conditions during sampling, each infant received no enteral feed and no more than 5 mg/kg/minute glucose intravenously for at least one hour before sampling. Samples were taken, once a day for the first postnatal week, by heelprick, the foot being sufficiently warm to allow free blood flow: 40 µl blood were added to 3% perchloric acid to denature enzyme activity; 50 µl plasma were also collected. Samples were analysed, using a Cobas fast centrifugal autoanalyser for glucose, gluconeoganic precursors (pyruvate, alanine, lactate, glycerol), ketone bodies (β-hydroxybutyrate and acetoacetate) and non-esterified fatty acids (NEFA).

Each infant's birth weight, head circumference (HC) and mid-arm circumference (MAC) was recorded. A birthweight SD score was calculated, which represented the number of SDs by which the infant's birth weight differed from the mean for gestational age. Birthweight centile charts used were those previously derived from Newcastle births.[12]

Data were analysed using the statistical package for the social sciences (SPSS X). χ^2 Tests were used to compare background data for groups of infants. As the blood metabolite concentrations did not have a normal distribution, Mann-Whitney U tests were used to compare metabolite concentrations between groups.

Ethical approval for the study was granted by the ethics committee of Newcastle Health Authority. Informed consent was obtained from parents for the inclusion of each baby in the study, and, as far as possible, sampling was coordinated with clinically necessary tests.

Results

Details of the groups of infants are given in table 1. There were no significant differences between the groups in terms of birth weight, gestation, or incidence of obstetric or perinatal problems (such as maternal smoking, instrumental delivery, cardiotocographic evidence of fetal distress, or infant's requirement for active resuscitation after birth). In particular, the severity of growth retardation, as measured by mean birthweight SD score and mean MAC:HC ratio, was similar for both groups. Once enteral or intravenous feeding was established, both groups received intravenous glucose and enteral feeds at similar rates on each postnatal day.

Results of metabolic investigations are shown in table 2. Infants of the absent EDV group had lower blood glucose concentrations at birth and in the first six hours after birth than those of the present EDV group (fig 1, some points are superimposed). Although this difference did not reach statistical significance for cord blood (p=0·08), the difference was highly significant subsequently (p<0·01). Concentrations of ketone bodies and non-esterified fatty acid were significantly lower for the absent EDV group at birth compared with the present EDV group, and NEFA concentrations were lower in the first six hours after birth (fig 2, some points are superimposed). For all infants,

Table 1 Details of infants studied

	Absent EDV (n=11)	*Present EDV (n=14)*	*p Value*
Median gestation (weeks)	35	37	0·076
Range	32–40	32–40	
Male:female ratio	8:3	5:9	0·151
Median birth weight (g)	1525	1903	0·065
Range	668–2020	859–2296	
Mean birth weight SD score (SD)	−3·22 (0·90)	−2·95 (0·54)	0·389
Mean MAC:HC (SD)	0·24 (0·02)	0·26 (0·03)	0·551

Table 2 Results of metabolic investigations (mmol/l)

	Absent EDV (n=11)	*Present EDV (n=14)*
Cord blood at delivery:		
Mean pH (SD)	7·31 (0·07)	7·31 (0·10)
Median NEFA (range)	0·08 (0·02–0·15)	0·31 (0·04–0·65)**
Median ketone bodies (range)	0·05 (0·03–0·16)	0·17 (0·06–0·36)*
Median TGS (range)	3·34 (1·33–5·57)	4·06 (1·50–6·70)
Median lactate (range)	2·70 (0·98–4·39)	3·58 (1·13–5·85)
Median glucose (range)	3·0 (2·5–4·2)	3·9 (2·5–5·8)
Heelprick blood at <6 hours		
Median NEFA (range)	0·18 (0·01–0·32)	0·85 (0·02–1·20)*
Median ketone bodies (range)	0·04 (0·01–0·08)	0·05 (0·01–0·11)
Median TGS (range)	3·57 (1·33–9·91)	3·95 (1·50–8·55)
Median lactate (range)	2·89 (0·98–8·40)	3·28 (1·13–7·40)
Median glucose (range)	2·0 (1·5–2·3)	3·0 (2·0–5·2)***

Mann-Whitney *p<0·05, **p<0·01, ***p<0·001
TGS=total gluconeogenic substrate

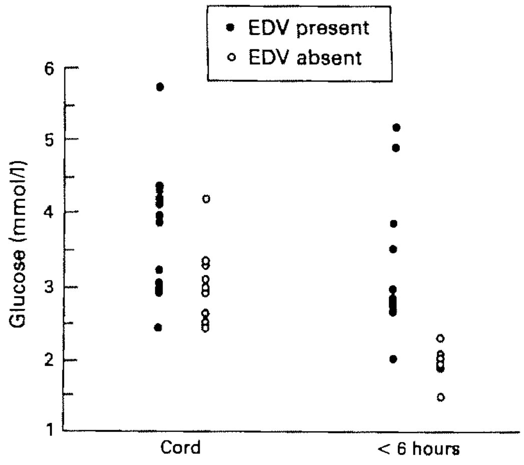

Figure 1 Blood glucose concentrations in infants with present or absent EDV.

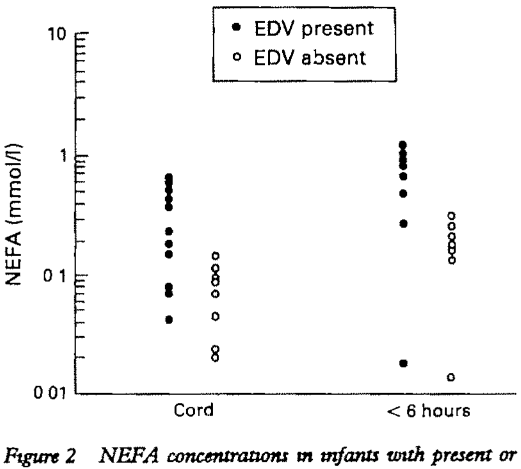

Figure 2 NEFA concentrations in infants with present or absent EDV.

concentrations of lactate and gluconeogenic substrates were high, but there were no differences between the present and absent EDV groups. After the first day there were no metabolic differences between the groups nor in the relationships between metabolic concentrations (ketone bodies/glucose; ketone bodies/NEFA).

Blood glucose concentration at birth and in the first hours of life was not related to gestational age in this study of 25 infants, considered as a whole, or when the groups were considered separately.

None of the infants, in either group, had symptoms of hypoglycaemia, namely convulsions or coma, and the two groups were indistinguishable in terms of clinical characteristics and postnatal complications.

Discussion

SGA infants with abnormal antenatal Doppler studies may be expected to be those at highest risk of metabolic derangement. Studies correlating antenatal fetal umbilical blood sampling and Doppler indices have suggested that the fetus with abnormal indices is more likely to be hypoglycaemic, hypoinsulinaemic, hypoxaemic, hyperlacticaemic and acidotic.[13 14] The degree of in utero asphyxia correlates with other metabolic derangements such as hypertriglyceridaemia[15] and alteration in amino acid metabolism.[16 17] The asphyxiated SGA fetus in utero does not mount a NEFA/ketone body response in the face of hypoglycaemia[15]; this abnormality thus predates the failure of such responses postnatally. However in these studies, the fetuses with abnormal Doppler were significantly smaller than those with normal Doppler, which casts doubt over the added predictive value of Doppler ultrasound over conventional assessment of fetal measurement.

The present study demonstrates that even in babies with similar degrees of moderate/severe growth retardation, umbilical arterial Doppler can distinguish a group of babies with metabolic maladaptation, and this is consistent with recent data on lactate concentrations in utero.[13] Such babies had significantly lower blood glucose concentrations in the first few hours after birth. However, as fetuses and neonates, these subjects failed to demonstrate a lipolytic response to low blood glucose concentrations. This correlates well with data obtained from antenatal fetal blood sampling,[15] and demonstrates that maladaptation extends into postnatal life. The data suggest that SGA infants with absent EDV were subject to reduced availability of the metabolic fuels which are important in the neonatal period. This may have had adverse neurological sequelae, even in the absence of major symptoms, but this study did not aim to investigate the clinical associations of such metabolic abnormalities.

On the other hand, it appears from the present study that SGA babies with EDV present on umbilical Doppler studies are likely to have normal metabolic profiles in the early neonatal period.

This study demonstrates the difficulties in identifying a well matched control group with normal Doppler studies, in that SGA fetuses with abnormal umbilical Doppler are likely to undergo elective early delivery. However, in the present study, the differences in gestational age between the groups were small and statistically insignificant. Moreover, the present study and a recent study[4] failed to find any influence of gestational age on metabolic adaptation in SGA babies. Therefore we feel that the small differences in gestational age were clinically insignificant.

There is evidence, in a recent study of a similar group of SGA infants, that the feeding regimens used were effective in maintaining adequate glucose concentrations.[4] In the present study, enteral and intravenous intakes were similar between the groups, and, once feeding was started, there were no differences between the groups in blood glucose concentrations or the number of occasions on which low blood glucose concentrations ($\leq 2 \cdot 6$ mmol/l) were found.

A larger study is recommended to determine the sensitivity and specificity of abnormal Doppler studies for evidence of intrauterine hypoglycaemia and postnatal metabolic derangement. For example, study groups of at least 26 each would be required to show a significant difference (with 95% confidence, SD for blood glucose concentration 0·9 mmol/l) of 0·5 mmol/l in umbilical venous blood glucose concentration between groups of infants with absent and present EDV. In addition, a follow up study of these babies may demonstrate whether long term neurological damage has been sustained.

We conclude that abnormal antenatal Doppler studies (namely absent end diastolic flow) predicted those SGA fetuses who were at increased risk of early postnatal hypoglycaemia, and it is possible that these fetuses had lower glucose concentrations antenatally, with failure to mount an appropriate lipolytic and ketogenic response. Equally important is the observation that the very small fetus (birth weight >2 SD below the mean) with normal Doppler studies was more likely to mount the appropriate metabolic adaptive responses. The damaging effects of neuroglycopenia in the absence of alternative fuels (because of poor counter-regulatory ability in these fetuses and neonates) need to be minimised in cases of severe growth impairment, as in this study. Delivery may be appropriate when antenatal Doppler studies are abnormal, provided the risks of preterm delivery do not outweigh the risks of intrauterine metabolic maladaptation. The monitoring of fetal glucose concentrations during delivery may help determine management.

In the first few hours after birth there was continued risk of severe hypoglycaemia and early adequate energy intake had to be ensured. However, after this age, infants with abnormal Doppler studies were at no greater risk of metabolic problems. It may be that provision of adequate parenteral and enteral energy outweighed the adverse effects of such antenatal risk factors.

Doppler studies predict metabolic maladaptation, and add to the information already available antenatally regarding fetal size. Therefore abnormal antenatal Doppler studies should alert the obstetrician to the fetus who is at risk in utero, and the paediatrician to the infant who will require close monitoring and the prevention of further metabolic stress.

Dr Hawdon was supported by the Scientific and Research Committee of Newcastle Health Authority and by a Foundation for the Study of Infant Deaths Training Fellowship. Mr Walkinshaw was in receipt of a Subspeciality Training Fellowship from the Royal College of Obstetricians and Gynaecologists.

We thank the parents who gave consent for the inclusion of their babies in the study, and hospital staff for their support and cooperation.

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Superior mesenteric artery blood flow velocity in necrotising enterocolitis

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Abstract

Doppler measurements of blood flow velocity were obtained from the superior mesenteric artery (SMA), coeliac axis, and anterior cerebral artery (ACA) of 19 infants with suspected necrotising enterocolitis, which was classified as confirmed (n=9) or unconfirmed (n=8). Infants with confirmed disease were compared with controls who were either enterally fed or who were receiving intravenous fluids.

SMA velocity was significantly higher in the infants with confirmed necrotising enterocolitis (36·5 cm/s) than in unfed controls (20·4 cm/s) or infants with unconfirmed enterocolitis (19·6 cm/s).

Three infants with confirmed disease had data from before the onset of symptoms. One had low SMA velocity on the first day of life, and one showed no increase in SMA velocity after enteral feeds were started.

SMA velocity is increased when infants develop symptoms of necrotising enterocolitis, suggesting that total gut ischaemia is not present at the time that the disease is clinically apparent, although it may precede the onset of symptoms and play a part in the pathogenesis of the disorder.

Epidemiological studies have suggested a bewildering variety of risk factors for necrotising enterocolitis. Identified risk factors include birth asphyxia,[1–4] chronic intrauterine hypoxia,[5 6] apnoea,[2 4 7 8] umbilical catheterisation,[1 4 7 9] respiratory distress and ventilation,[4 7 8] patent ductus arteriosus,[3] polycythaemia,[8 10] hypoglycaemia,[8] and hypothermia.[10] It is widely believed that intestinal ischaemia is the unifying mechanism that explains the ability of these many different factors to injure the neonatal bowel. Risk factors might cause ischaemia directly or as a consequence of the 'diving reflex' when blood flow is diverted from the abdominal organs during hypoxia, thus preserving cerebral oxygenation.

However, the concept of necrotising enterocolitis being predisposed to by gut ischaemia is not straightforward. Clustering of cases has been used to support the idea of an infective aetiology.[11] Although many agents, including bacteria and viruses, have been implicated in some outbreaks,[12] other studies have not identified infective agents to be consistently associated with necrotising enterocolitis.[7] It has also been proposed that mucosal immaturity alone may be the most important factor in its aetiology.[13 14] The fact that necrotising enterocolitis is rare in the absence of enteral feeding demonstrates the importance of intraluminal factors. Breast milk exerts a protective effect whereas hyperosmolar feeds,[2] or hyperosmolar drugs such as high doses of vitamin E,[15] may be risk factors.

In order to examine the hypothesis that necrotising enterocolitis is due to intestinal ischaemia, Doppler ultrasound has recently been used to study the characteristics of blood flow in the superior mesenteric artery of infants in high risk groups. We have demonstrated a specific reduction in superior mesenteric artery (SMA) blood flow velocity in infants who are small for gestational age, who experienced chronic intrauterine hypoxia[16]; and Coombs *et al* have shown absent diastolic flow and reduced velocity in infants with patent ductus arteriosus.[17] However, none of the infants in these studies went on to develop necrotising enterocolitis.

We therefore set out to measure SMA blood flow velocity using Doppler ultrasound in infants who developed necrotising enterocolitis. By studying from birth a large number of infants who were at risk we also hoped to have data that preceded the onset of this condition in a number of infants. In order to document the specificity of our findings for the mesenteric circulation, we also measured velocity in the coeliac axis and anterior cerebral artery (ACA).

Methods

SUBJECTS WITH NECROTISING ENTEROCOLITIS

The criteria of the British Association of Perinatal Medicine (BAPM) were used to define cases of suspected necrotising enterocolitis which occurred on our unit over a two year period.[18]

A total of 19 infants were studied. To be classified as a case of suspected necrotising enterocolitis an infant must have had at least two of the following features: abdominal distension, blood in the faeces, a distinct clinical deterioration (hypotonia, lethargy, or apnoea), or increased intraluminal gas visible on an abdominal radiography. The characteristics of these infants are shown in table 1.

Confirmed cases

Nine infants were subsequently confirmed to have necrotising enterocolitis on the basis of radiological findings (intramural gas, hepatic portal venous gas), surgery or postmortem

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Accepted 9 March 1992

Table 1 Characteristics of the infants with suspected necrotising enterocolitis

Cases	*Sex*	*Gestation (weeks)*	*Birth weight (kg)*	*Postnatal age (days)*	*Mean blood pressure (mm Hg)*	*Last enteral feed†*	
						Hours before	*% intake*
Confirmed cases:							
1	F	24	762	12	29	—	—
2	F	26	902	25	51	1	100
3	M	28	1248	6	46	15	100
4	F	28	1436	10	46	85	100
5	F	29	1150	8	19	—	—
6	F	30	1040*	44	64	30	100
7	F	34	1220*	6	—	24	100
8	F	36	2990	22	63	28	100
9	M	39	3180	1	—	8	100
Mean		30·4	1550	15	45·4		
SD		4·9	890	13·4	16·6		
Suspected, unconfirmed cases							
10	M	23	510	8	28	—	—
11	F	24	680	14	60	—	—
12	F	24	720	26	36	32	100
13	M	26	920	14	34	—	—
14	M	28	1246	6	43	—	—
15	F	29	516**	9	—	40	50
16	F	32	666**	26	—	79	100
17	M	32	1180**	12	66	—	—
Mean		27·3	810	14	44·4		
SD		3·6	280	7·8	15·2		
Cases with other pathology:							
18	M	27	1118	13	44	26	100
19	M	28	1100	12	30	13	43

Infants who were small for gestational age are indicated * birth weight <10th centile for gestation; ** <3rd centile. See text for further details † Where no figure given, the infant had no enteral feeds

findings, in accordance with the BAPM criteria. One infant (case 3) was a surviving twin whose cotwin was a miscarriage some weeks before delivery. Another (case 8) was born with a diaphragmatic hernia, which had been surgically repaired on the first day of life. There was a term infant (case 9) whose mother had admitted to abusing a number of drugs during pregnancy. Only one infant (case 1) had an umbilical arterial catheter in place at the time of measurement, and only two had positive blood cultures (case 1, *Candida albicans;* case 7, *Staphylococcus aureus*).

Cases with other abdominal pathology

Two infants had proved intra-abdominal pathology other than necrotising enterocolitis: one was found to have an ileal perforation in association with a meconium plug, and the other had intestinal infarction from an aortic thrombus, obstructing the coeliac and mesenteric arteries. (These two constitute the 'other abdominal pathology' group.)

Table 2 Characteristics of the control infants

Controls	*Gestation (weeks)*	*Birth weight (g)*	*Postnatal age (days)*	*Mean blood pressure (mm Hg)*
Controls on intravenous fluids				
1	25	768	7	36
2	26	910	9	53
3	28	1164	9	—
4	29	1510	11	57
5	30	1300	9	—
6	30	1026*	7	45
7	34	1260**	7	—
8	40	3482	5	60
9	42	3482	2	—
Mean	31·6	1656	7·3	50·2
SD	6·0	106	2·6	9·7
Enterally fed controls				
1	25	870	13	—
2	26	966	28	—
3	27	942	16	—
4	28	1038	7	—
5	30	1506	8	—
6	30	946*	8	—
7	36	1798**	9	—
8	34	1980	14	56
9	41	3910	1	—
Mean	30·8	1500	12	
SD	5·3	980	7·6	

Infants who were small for gestational age are indicated *birth weight <10th centile for gestation, **<3rd centile

Suspected, unconfirmed cases

Of the remaining eight infants, six were found to be septicaemic (case 10, *C albicans*; cases 11 and 15, *Klebsiella* sp, cases 12 and 17, *Staphylococcus epidermidis*; case 13, enterobacter), one was severely growth retarded and thought to have meconium plugging, and in one the cause of his deterioration was not identified.

Mean birth weight was significantly lower in the group with unconfirmed necrotising enterocolitis, with three having a birth weight less than the third centile for gestation.

CONTROLS

For each infant with confirmed necrotising enterocolitis, control data were selected from Doppler measurements performed on babies enrolled in other studies, who had not suffered from gastrointestinal problems or birth asphyxia. Data from a pool of 80 infants were available for matching. Control data were matched for postnatal age, the birth weight and gestation of the infant, and the degree of intrauterine growth retardation. For each index case we selected one control who was receiving enteral feeds, and one who was receiving intravenous fluids only, giving two control groups. The characteristics of the control infants are shown in table 2.

MEASUREMENTS

Measurements of blood flow velocity and pulsatility index were obtained from the SMA, coeliac axis, and ACA as previously described.[16] The artery was visualised in real time and range-gating used to sample pulsed wave Doppler signals from the particular artery under study. All readings were corrected for the angle of insonation. The measurements were obtained after the onset of symptoms during the acute phase of the illness.

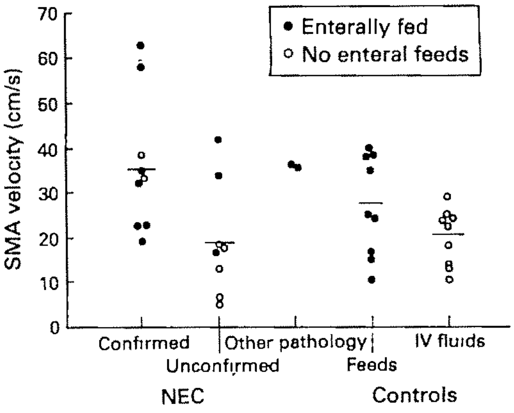

Figure 1 Blood flow velocity in the SMA for individual infants with suspected necrotising enterocolitis (NEC), and for infants in the control groups, receiving enteral feeds or intravenous (IV) fluids.

Table 3 Mean (SD) of velocity and pulsatility index in the SMA, coeliac axis, and ACA for the main groups

	Velocity (cm/s)			*Pulsatility index*		
	SMA	*Coeliac axis*	*ACA*	*SMA*	*Coeliac axis*	*ACA*
NEC: confirmed	36·5 (15·3)	39·9 (9·8)	19·1 (9·2)	2·17 (0·9)	1·58 (0·5)	2·20 (2·4)
NEC, suspected, unconfirmed	19·6* (12·9)	33·1 (15·4)	19·3 (9·0)	2·99 (1·7)	1·69 (1·1)	1·67 (0·8)
Controls: enterally fed	27·4 (11·2)	36·5 (14·0)	19·7 (6·4)	2·56 (0·9)	1·75 (0·8)	1·64 (0·5)
Controls, on IV fluids	20·4** (6·4)	38·5 (15·3)	19·8 (2·3)	2·72 (1·0)	1·39 (0·5)	1·36 (0·4)
Controls: combined	23·9 (9·3)					

Significant differences between the confirmed necrotising enterocolitis (NEC) group and the other groups are shown (*=p<0·05;**=p<0·01).
IV, intravenous.

Data from the infants with confirmed necrotising enterocolitis were compared with the data from the other groups using unpaired *t* tests. Variance ratios (F) were used to compare the variances of cerebral artery velocities.

Results

DATA AT THE TIME OF SYMPTOMS

Mean SMA velocity was significantly higher in the infants with confirmed necrotising enterocolitis (36·5 cm/s) than in infants with suspected, unconfirmed disease (19·6 cm/s, p<0·05; fig 1, table 3). SMA velocity was also significantly higher in the confirmed group than in the control group receiving intravenous fluids (20·4 cm/s, p<0·05). Although mean SMA velocity was slightly higher in infants with confirmed disease than in the control group receiving enteral feeds (27·4 cm/s), this difference was not significant.

When the two control groups were combined, SMA velocity was still significantly lower in these infants than in infants with confirmed necrotising enterocolitis (p<0·05).

There were no significant differences between the groups in mean coeliac or cerebral artery velocities. However, there was a much greater variation in cerebral artery velocity in the groups of infants with confirmed and suspected necrotising enterocolitis compared with the group of controls on intravenous fluids (confirmed: F=15·9, p<0·001; unconfirmed: F=15·2, p<0·001).

There were no statistically significant differences in pulsatility index between the groups.

PROSPECTIVE DATA

Prospective data obtained from three infants with confirmed necrotising enterocolitis is shown in fig 2. The first of these (case 2) had only one measurement performed, some time before the onset of necrotising enterocolitis. SMA velocity was normal at this stage.

The second infant (case 3) was the survivor of a twin pregnancy where the other twin was a miscarriage. SMA velocity was initially normal but did not increase after the introduction of enteral feeding at 3 days of age. When he developed necrotising enterocolitis at 6 days the SMA velocity was very high. After treatment this returned to normal, and when feeds were recommenced there was an increase in SMA velocity.

The third infant (case 7) was growth retarded and had a very low SMA velocity on day 1 (the lowest day 1 value we have obtained from a very low birthweight infant). This rose to a normal value by day 3, 24 hours after the introduction of enteral feeds. On day 6, when she developed necrotising enterocolitis, the SMA velocity stayed at a relatively high level even after feeds were stopped.

Prospective data were also obtained from four infants with suspected, unconfirmed necrotising enterocolitis. In two infants the values were normal (cases 10 and 14), in one there was no increase in SMA velocity when feeds were introduced (case 15) and in one there was a low SMA velocity on day 1 (case 16).

Discussion

By the time that symptoms were apparent, SMA blood flow velocity was significantly higher in infants with confirmed necrotising enterocolitis than in unfed controls. SMA velocity was also higher in confirmed cases than in infants with suspected but unconfirmed disease. Mean SMA velocity was slightly (but not significantly) higher in the infants with necrotising enterocolitis than in controls receiving enteral feeds.

There are a number of possible explanations for the differences in velocity between confirmed and suspected cases. There were

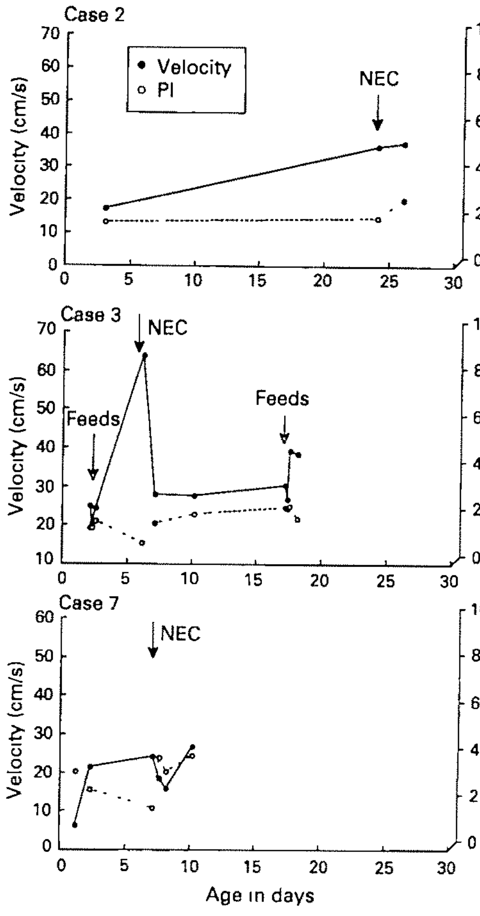

Figure 2 Blood flow velocity and pulsatility index (PI) from the SMA of the three infants with confirmed necrotising enterocolitis (NEC) who had prospective data.

more infants who were small for gestational age in the unconfirmed group. We have previously demonstrated growth retardation to be associated with lower SMA velocity.[16] Fewer of the unconfirmed group had received enteral feeds at any stage in their life, and enteral feeding has been shown to increase SMA velocity even in premature infants.[19 20] More were septicaemic, and these findings may represent the effect of septicaemia on SMA velocity. Finally, there may be a raised SMA blood flow velocity in the infants with confirmed necrotising enterocolitis, but not in those with unconfirmed disease, because the disorders are unrelated.

Were infants who were not receiving enteral feeds appropriate controls for the infants with necrotising enterocolitis? None of the index cases was receiving enteral feeds at the time that the measurements were made, and all had their stomachs aspirated via a nasogastric tube. Two had never received any feeds enterally, but in the other seven the time elapsed since the last feed varied between 1 and 85 hours. Infants whose feeds had been stopped would have been expected to have had gastrointestinal blood flow velocity somewhere between the levels found in fed and unfed infants, but it is not known how quickly or to what extent blood flow decreases after stopping feeds. Even when the two control groups were combined, velocity was significantly higher in the infants with confirmed necrotising enterocolitis Although previous enteral feeding may account for some of the observed increase in SMA velocity, it would not account for it all.

Why should necrotising enterocolitis produce an increase in SMA velocity? If a baby is operated upon, the serosal surface of unaffected bowel is often noticed to be inflamed; the increased SMA velocity in necrotising enterocolitis could therefore result from an inflammatory response in the remaining 'healthy' bowel. Prospective data showed a very low SMA velocity in one infant (case 7) five days before the onset of symptoms. It is possible that an ischaemic insult to the gut may precede the onset of necrotising enterocolitis, with the increase in SMA velocities at the time of clinical presentation representing a postischaemic hyperaemia. A reduction of vessel diameter could produce an increase in velocity without any increase in volume flow, but using ultrasound imaging we saw no evidence of arterial thrombosis in any of the infants with confirmed disease, and only one of these infants still had an umbilical catheter in place. All measurements were taken from the SMA close to its origin from the aorta, a location where active changes in vascular diameter are unlikely.

Data showing a low SMA velocity, or a lack of response to enteral feeding, before the onset of necrotising enterocolitis may indicate a mechanism predisposing to this condition. However, both of these findings were also noted in growth retarded infants who had suspected but unconfirmed disease. Clearly there must be other factors operating which determine which infants will develop confirmed disease.

There was a significantly greater variation in cerebral artery velocities in both of the necrotising enterocolitis groups, compared with the controls, although there was no difference in mean velocity. The diversion of cardiac output into a mesenteric circulation which has a fixed high blood flow might disturb the regulation of blood pressure and cerebral blood flow.

SMA blood flow velocity is probably increased, and certainly not reduced, at the time infants develop necrotising enterocolitis. It is therefore unlikely that an overall reduction in gut blood flow is responsible for the progression of the disease, although localised factors may affect discrete areas of bowel. However, low total gut blood flow may have a causative role early in the pathogenesis of the disease, before any symptoms develop.

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Archives of Disease in Childhood 1992, 67: 797–801

Development of cutaneous microflora in premature neonates

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Abstract

Coagulase-negative staphylococci (C-NS) are a frequent cause of bacteraemia in premature neonates. It is likely that the strains of C-NS causing bacterial sepsis in premature neonates have their origin on the patient's skin surface. We have studied the quantitative development of the skin microflora at eight sites on premature neonates.

A swab wash method was used to sample and enumerate the cutaneous microflora of premature neonates admitted to an intensive care unit with respiratory distress syndrome. The numbers of bacteria present on the skin increased rapidly by 100-fold in the first week of life. The species of C-NS found on neonatal skin were similar to those found on adult skin. However, the bacterial population was 10^3 lower by comparison. There was considerable variation in numbers of bacteria and in the proportion resistant to antibiotics from day to day. There appeared to be no association between antibiotic usage and the proportion of isolates resistant to antibiotics, although the resident bacteria were in many cases resistant to a variety of antibiotics. C-NS were isolated from 92% of samples from which bacteria were isolated. *Staphylococcus epidermidis* was found at all sites and accounted for 82% of each colonial type of staphylococcus isolated. Other organisms isolated included *Propionibacterium* sp, α-haemolytic streptococci, aerobic spore-bearing bacilli, aerobic coryneforms, *Candida albicans, Klebsiella oxytoca, Pityrosporum* sp, *Klebsiella pneumoniae,* and *Escherichia coli.*

The results of this study suggest that the skin of premature neonates is colonised with antibiotic resistant C-NS during the first week of life and that the chance of contamination of an intravascular catheter at insertion increases during this period.

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Accepted 7 January 1992

Coagulase-negative staphylococci (C-NS) are frequent isolates from blood cultures of premature neonates.[1 2] Episodes of bacteraemia with C-NS are usually associated with intravascular catheters[3] and diagnosed after the first week of postnatal life.[2] Intravascular catheters predispose to bacteraemia with C-NS both by providing a break in the cutaneous barrier and by acting as a foreign body, reducing local resistance to infection. Quantitative blood culture techniques have shown that numbers of C-NS present in blood of premature neonates with bacteraemia may exceed 1000 colony forming units (cfu)/ml.[4 5] Defective opsonisation and phagocytosis may allow these large numbers of C-NS to circulate in the blood.[6]

The strains of C-NS most frequently associated with neonatal infection are often resistant to a wide range of antimicrobials.[7] Antibiotic resistant C-NS spread from patient to patient via the hands of nursing and medical staff, leading to colonisation of the skin of premature neonates in intensive care units within the first week of life. The numbers of bacteria on the skin surface will determine the probability and degree of contamination of the catheter at the time of insertion. Local immune defences are more likely to be overcome when large numbers of bacteria are present on the skin at the catheter insertion site.

Qualitative studies suggest that the skin of premature neonates becomes colonised with C-NS within the first few days of life.[8] However, the quantitative development of the cutaneous microflora has not been studied. This is due in part to unsuitability of methods of skin sampling which have been developed primarily for use on adults and may damage the skin of neonates. In this study we have used a non-traumatic swab wash method[9] to study the quantitative and qualitative changes in the bacterial flora and in the level and pattern of antibiotic resistance of these bacteria. This method of sampling gives comparable results in full term neonates and adults to those obtained with the scrub wash method of Williamson and Kligman.[10]

Patients and methods

SAMPLING OF CUTANEOUS MICROFLORA

Nine premature neonates admitted to the Peter Congdon Regional Neonatal Unit, The General Infirmary, Leeds, between 25 January and 21 April 1990 with respiratory distress syndrome were sampled. The gestational age range was 25–32 weeks with birth weight ranging from 680 to 1920 g. Neonates were selected on the basis of prematurity only (<33 weeks' gestation). The following sites were sampled using a swab wash method[9]: forehead, chest, periumbilical region, back, upper and lower arm, and upper and lower leg. Neonates were sampled within six hours of birth, on days 3, 5, 7, and weekly thereafter. Local ethical committee approval was obtained for this study. Informed consent was obtained from the parents of each infant sampled.

QUANTITATION OF MICRO-ORGANISMS IN WASH FLUIDS

Samples were serially diluted 10-fold in half strength wash fluid. Each dilution was vigorously mixed, and 100 μl volumes of diluted and undiluted wash fluid were spread over the surface of the following selective and non-selective media: heated 5% (v/v) horse blood agar (CM 55: Oxoid) incubated at 37°C in air for four days; Sabouraud dextrose agar (Oxoid CM 41) with chloramphenicol (50 mg l) incubated at 37°C in air for seven days; 5% (v/v) horse blood agar with neomycin (final concentration 28 mg/l) incubated at 27°C anaerobically for seven days; aerobic coryneform agar with and without furazolidone (6 mg/l) incubated at 37°C aerobically for two days[11]; reinforced clostridial agar with and without furazolidone incubated at 37°C for seven days anaerobically[11]; and pityrosporum agar[12] incubated at 34°C aerobically in a moist chamber for 14 days. After incubation, colonies were enumerated with a colony counter (Gallenkamp CNW325010X) to give a total viable count expressed as cfu/cm^2 and then logarithmically transformed.

IDENTIFICATION OF ORGANISMS

Preliminary identification of staphylococcal species was based on colonial morphology, positive catalase test, slide coagulase test, and plate DNAse test.[13] One colony of each colonial type was identified as to species by the scheme of Kloos and Schleifer.[14] Catalase negative Gram positive cocci were identified on the basis of haemolysis and growth at 45°C. Aerobic coryneform bacteria were infrequently isolated and were not differentiated further. Gram negative rods were identified using the API 20E enterobacteriaceae biochemical typing system. Yeasts growing on pityrosporum agar were confirmed as *Malassezia furfur* species by colonial appearance and microscopic morphology. Yeasts isolated on Sabouraud dextrose agar were tested for the ability to form germ tubes (isolates were examined microscopically for germ tube formation after incubation for two hours in horse serum). Germ tube positive isolates were identified as *Candida albicans*, whereas germ tube negative isolates were grouped as *Candida* sp. Propionibacteria were identified on the basis of colony and Gram stain morphology and classified as to species as described by Holland.[15]

PROPORTION OF CUTANEOUS FLORA RESISTANT TO ANTIBIOTICS

In order to determine directly the sensitivity of bacterial skin isolates to six antimicrobial agents, antibiotics were incorporated at the following concentrations into Isosensitest (Oxoid) agar plates:vancomycin 4·0 mg/l, gentamicin 0·5 mg/l, erythromycin 2·0 mg/l, methicillin 2·0 mg/l, penicillin 1·0 mg/l, and chloramphenicol 32·0 mg/l.

Then 100 μl of swab wash fluid was plated onto each media. The numbers of colonies growing on each of the antibiotic-containing plates, with reference to colony counts on media containing no antibiotics, was used to calculate the percentage of the bacterial population that was sensitive to each antibiotic.

DETECTION OF ANTIMICROBIAL SUBSTANCES IN SAMPLE FLUIDS

The presence of antimicrobial substances in skin wash fluid samples was detected by pipetting 100 μl of the sample into wells previously cut in Isosensitest agar plates that had been surface seeded with Oxford staphylococcus (NCTC 6571). Detection of gentamicin in wash fluid samples was by colorimetric assay using a TDX antimicrobial assay machine (Abbott).

HAND IMPRESSION PLATES

At each sampling a horse blood agar (Oxoid) hand impression plate was taken of the attendant nurses' finger pads and nail margins.

Results

The swab wash method allowed repeated sampling without trauma to fragile neonatal skin. However, daily sampling was not performed in case this disrupted normal skin flora development. No adverse effects on neonatal skin were noticed during the study period.

Acquisition of skin flora followed the same pattern in the four neonates born vaginally after normal labour and in the five neonates born by caesarean section. A surprising observation was the lack of vaginal flora and enterobacteriaceae in early swab wash samples from infants born vaginally.

Bacteria were detectable on the skin surface within six hours of birth. The most common bacterial isolates during the study were C-NS. C-NS were isolated from 92% of samples containing bacteria. Organisms other than C-NS were infrequently isolated from single sites. These organisms were probably not part of the developing microflora and at no time did they replace staphylococci as predominant flora. Other organisms isolated from swab wash samples were: *Propionibacterium* sp, α-haemolytic streptococci, aerobic spore bearing bacilli, aerobic coryneforms, *C albicans, Klebsiella oxytoca, Pityrosporum* sp, *Klebsiella pneumoniae,* and *Escherichia coli.*

Numbers of staphylococci present at the skin sites sampled rose rapidly during the first 7 days of postnatal life (fig 1). Acquisition of cutaneous C-NS in neonates of ≤28 weeks' and >28 weeks' gestational age followed a similar pattern.

During the study 2548 staphylococcal isolates were selected by colonial morphology for species identification. *Staphylococcus epidermidis* was found at all sites and accounted for 82% of the total colonial types of staphylococci. Other species of staphylococcus isolated were: *S warneri* 4·2%, *S haemolyticus 1* 4·1%, *S aureus* 2·4%, *S saprophyticus* 1·6%, *S hominis 1*

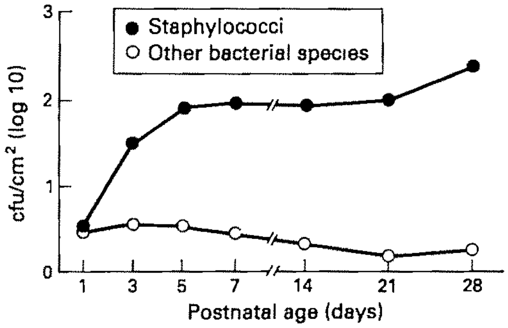

Figure 1 Quantitative changes in cutaneous microflora with postnatal age. Measurements are logarithmically transformed and taken at eight sites in nine neonates

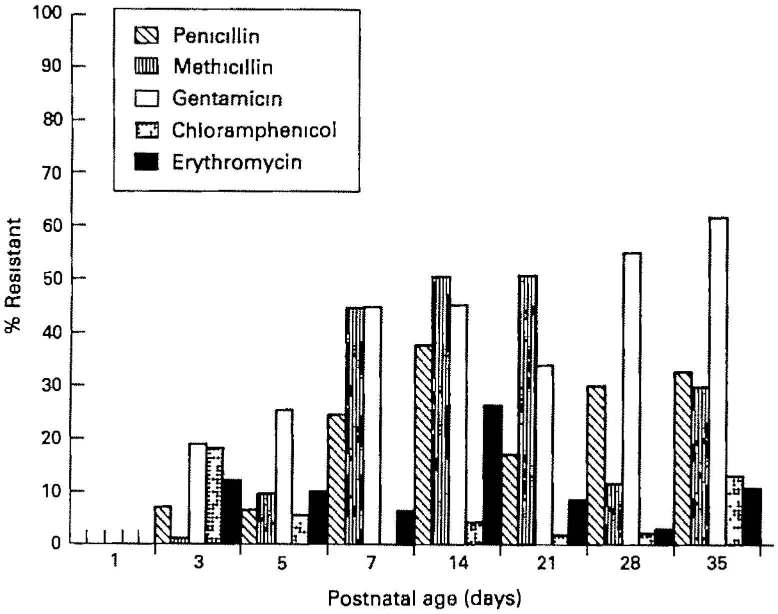

Figure 2 Changes in percentage of cutaneous staphylococci resistant to antibiotics with postnatal age. Measurements taken in all neonates at all sites.

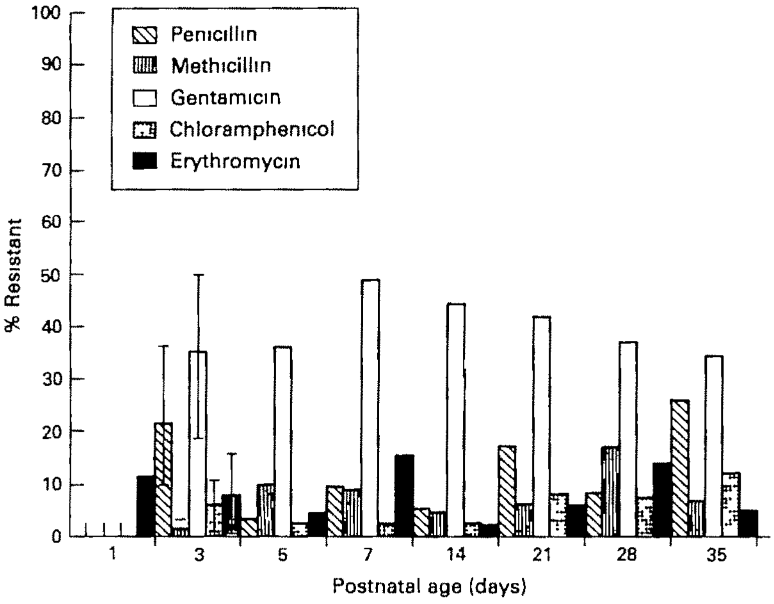

Figure 3 Changes in percentage of cutaneous staphylococci resistant to antibiotics with postnatal age. Measurements taken on the forearm in all neonates showing SD on day 3

0·8%, *S hominis 2* 0·7%, *S haemolyticus 2* 0·6%, *S xylosis 1* 0·5%, *S capitis* 0·4%, *S cohnii* 0·3%, *S xylosis 2* 0·2%, and *S simulans* 0·03% and micrococcus 2·0%. This rapid development of cutaneous microflora was unstable, with considerable day to day variation in numbers (0–1×10^3 cfu/cm^2) and in species present. A similar pattern of variation was seen in all neonates at all sites.

The proportion of C-NS resistant to antibiotics, determined by comparison of bacterial counts of swab wash samples on media with and without added antibiotics, revealed similar day to day variation (fig 2). Antibiotic resistant C-NS were present in all neonates by the end of the first week of life. Resistance to antibiotics used on the unit was an expected finding. However, resistance to antibiotics not commonly used, such as chloramphenicol, was also observed. The development with time of the percentage of cutaneous staphylococci from the forearm that were resistant to antibiotics is shown in fig 3. The forearm was chosen as an example as it is here that peripheral intravenous catheters are often sited.

The high proportion of isolates resistant to gentamicin was a common finding in all neonates at all sites. Quantitative changes in cutaneous staphylococci and percentage resistance to antibiotics with postnatal age is shown in one premature neonate in fig 4. Antibiotic resistance of the skin microflora did not appear to be temporally related to the use of antibiotics. Generally there was a wide variation in numbers and types of organisms with no correlation of species with site.

Antimicrobial activity on neonatal skin was demonstrated in 14·1% of 320 unselected swab wash samples. The finding of gentamicin in one swab wash fluid was probably due to gentamicin excreted in urine which contaminated the skin. A swab wash fluid exhibiting antimicrobial activity which was neutralised with the addition of β-lactamase solution was also noted. The finding of antimicrobial activity was not related to site of sampling.

The hand impression plates obtained from attending staff usually yielded C-NS, which were identified by the methods mentioned earlier. On one occasion *S xylosis 1*, an uncommon isolate, was detected on both neonatal skin and attendant's hand plate, suggesting transfer of organisms between the two.

Discussion

C-NS are the most frequent blood culture isolates from premature neonates in many intensive care units. Episodes of bacteraemia with C-NS are usually associated with intravascular catheters and it is likely that these devices provide the focus of infection from which bacteraemia develops.[3] An association between microbial numbers on the skin and the development of cannula related infection has been postulated.[16] *S epidermidis* is the species most often associated with neonatal infections and in this study accounted for 82% of the total colonial types isolated. Blood culture isolates

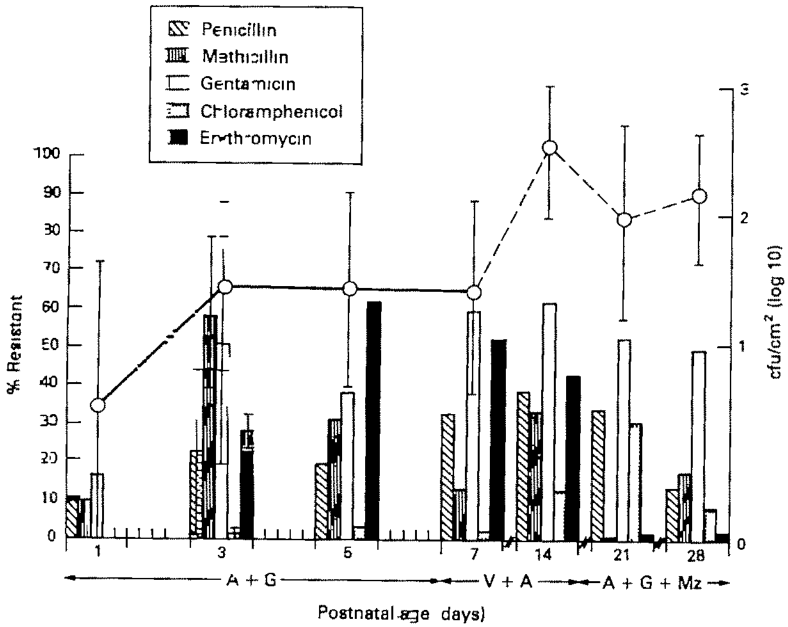

Figure 4 Quantitative changes in cutaneous staphylococci and percentage resistant to antibiotics with postnatal age. Resistance is shown in relation to treatment: ampicillin (A) and gentamicin (G) given to day 6, the vancomycin (V) and ampicillin, followed by ampicillin, gentamicin, and metronidazole (Mz).

of C-NS are usually resistant to a wide range of antibiotics.[7] In this study antibiotic resistant C-NS were isolated from the skin of premature neonates within days of admission to the neonatal intensive care unit.[8] This finding is possibly due to handling. C-NS were the most common isolates from neonatal skin in this study and *S epidermidis* the most frequent species.

Previous studies of bacterial colonisation of neonates have concentrated on sampling the anterior nares, axilla, and umbilicus of mature neonates and have not quantified bacterial numbers.[8] In this study the cutaneous microflora at eight sites were quantified, including sites used for intravascular catheter insertion. A number of factors might be expected to influence the numbers of C-NS on the skin of neonates, including nutrient availability, prolonged occlusion, environmental humidity and temperature, type of incubator, exposure to ultraviolet light (phototherapy) and antibiotics, topical disinfectants, pH and redox potential at colonised sites, and nursing practices.[17]

The flora of normal human skin in both children and adults does not vary widely from day to day and, with the exception of changes occurring at puberty, is extremely stable. This would indicate that the skin environment is also stable. In contrast, the variation and the relatively low numbers of skin microflora in this study (counts on adult skin may be 10^4–10^5 higher[8]) indicate that the skin of premature neonates is not supportive of a stable microbial ecosystem.

The skin environment of premature neonates appears only able to sustain low numbers of staphylococci and does not have the morphological or nutritional value to support other micro-organisms. Also, by contrast with findings in adults, there was no consistent pattern of site to site variation in bacterial numbers and there was no association of species of C-NS with specific sites.[19]

There was considerable variation in the antibiotic sensitivity pattern and biotype of isolates of C-NS obtained from the same neonate from one sampling to another, suggesting that the cutaneous microflora of premature neonates in the first month of life changes rapidly. It is likely that the microflora of premature neonates' skin is maintained in an erratic fashion by repeated inoculation due to the continual handling by attendant staff, and consists of a multiple transient flora which is reinoculated each time the neonate is handled. This hypothesis is supported by the findings of relatively few organisms, occasions when no organisms were detected at a site where organisms were previously isolated, and fluctuation in antibiotic resistance patterns not related to antibiotic use.

Possible factors preventing the stability of skin micro-organisms include the structure of the skin in the first weeks of life,[20] the presence of soluble factors on the skin inhibiting the growth of micro-organisms, or desiccation. Further work may help to determine when a stable microflora is established.

Antibiotic resistant strains of C-NS are more likely to be isolated from the skin of hospital patients than from people in the community.[21] Antibiotic resistant staphylococci isolated in this study may have been derived from (a) the hands of hospital staff, (b) from the bowel flora and inoculated onto the skin from faecal contamination, or (c) a combination of both.

Handling by medical and nursing staff will spread bacteria from site to site. It was not possible to correlate organisms found on the neonates' skin and hand carriage by attendant staff. Skin maturity did not appear to be a factor in acquisition of skin microflora, as development of the cutaneous microflora was similar in neonates of less than 29 weeks' gestational age to those of 29 or more weeks' gestational age. Enterobacteriaceae and yeasts were isolated infrequently, not related to any clinical signs and probably reflected intermittent hand carriage by attendant staff.

A high proportion of isolates of C-NS in this study were resistant to antibiotics including antibiotics not commonly used (such as chloramphenicol). This may be due to linkage of genes coding for resistance to antimicrobials on the same plasmid. In this study there seemed to be no association between the resistance patterns seen and the degree of resistance in the population to the antibiotics in use. Gentamicin was detected in some of the swab wash samplings, perhaps as a result of contamination of the skin with urine containing high concentrations of excreted gentamicin.

Bacteraemia with C-NS is uncommon in the first week of life.[2] We have found that the numbers of C-NS present on the surface of the skin increase during the first week of life. High concentrations of C-NS present on the skin surface at the time of catheter insertion will increase the chance of catheter tip contamination and the subsequent probability of bacterial invasion between the catheter and the thin skin of premature neonates.

These findings highlight the need for good skin preparation with an efficient skin disinfectant before inserting intravenous catheters and, as repopulation of the skin at the entry site occurs within 18 hours,[22] for site care after insertion. Good handwashing technique and minimal handling will help reduce the hand carriage and transfer of microorganisms.

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Archives of Disease in Childhood 1992; 67: 802–807

Complement activation in neonatal infection

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Accepted 17 December 1991

Abstract

To investigate the usefulness of indices of complement activation in the diagnosis of infections in the neonatal period, activation products C4d, Ba, and C3d were measured in 42 babies with a putative diagnosis of infection based on clinical/laboratory criteria, and compared with conventional clinical and haematological criteria of infection and with C reactive protein. The diagnosis of sepsis was confirmed by culture and identification of organisms in 17. Fourteen babies in whom infection was not suspected formed the control group. In babies with proved infection, concentrations of the fragments C4d, Ba, and C3d were higher than in babies with suspected infection in whom microbiological tests were negative, and concentrations of Ba and C3d were higher than in controls. C reactive protein and the platelet count were not significantly different in babies with proved infection and those with negative microbiological tests, but in the latter, C reactive protein concentrations were higher than in controls. Of the indices studied, high concentrations of Ba predicted microbiologically proved infection with the highest sensitivity (47·1%) and specificity (92·0%). Ba thus seems to be useful as an early indicator of infection in the neonatal period.

Bacterial infections in the neonatal intensive care unit are a major cause of morbidity and mortality.[1–3] The early and reliable diagnosis of sepsis in the neonate remains an important goal, but to date no single marker of infection, apart from culture and isolation of the relevant micro-organism, has been identified. Microbiological screening has the disadvantage of requiring 24 to 48 hours to provide results, while potentially life threatening neonatal infections must be treated immediately. Other, more indirect markers of infection, such as the white cell, platelet, and neutrophil counts and C reactive protein concentrations, have been shown to provide some diagnostic help,[4–10] but do not vary solely in response to the presence of infection.[6, 11–13]

The complement system is comprised of a series of over 30 proteins which are an essential component of host protection against a range of pathogenic organisms.[14] The complement cascade is activated directly by bacteria and antigen-antibody complexes, and the degree of complement activation could, therefore, provide early and specific evidence of bacterial infection (fig 1). To examine the possibility that triggering of the complement cascade reflects the presence of infection in the neonatal period, we studied the concentrations of complement fragments released during complement activation using techniques recently developed in our department.[15–17] The efficacy of complement activation in distinguishing infected from non-infected neonates is compared with other widely used indicators such as the platelet, neutrophil, and white cell counts and the concentration of C reactive protein.

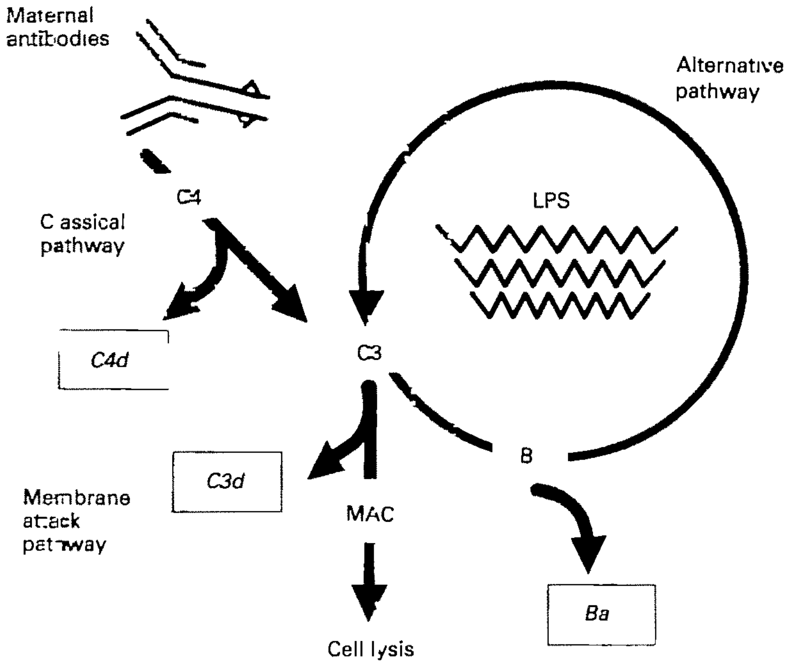

Figure 1 Complement activation pathway. Classical pathway activation in the neonate could be initiated by immune complexes composed of maternal antibody and bacterial antigen. The alternative pathway is activated by lipopolysaccharides (LPS) in bacterial cell walls. Both pathways converge at the level of C3 and the membrane attack pathway leads to formation of the membrane attack complex (MAC). Concentrations of the activation products C4d, Ba, and C3d provide a measurement of complement activation through the classical, alternative, and membrane attack pathways, respectively.

Subjects and methods

STUDY DESIGN

Babies included in this study were allocated to two main diagnostic groups: the controls, comprising a group of babies without suspicion of infection from whom blood was being taken for management purposes, and babies with the diagnosis of infection. The clinical/

laboratory criteria for this diagnosis are given in table 1 and were assessed independently by two physicians (GL and HG), who were unaware of the outcome of microbiological tests, complement measurements, or C reactive protein concentrations. On the basis of these criteria, babies with suspected infection were further subdivided into those in whom infection was considered to be probable and those in whom it was only considered possible. All babies with suspected infection – possible or probable – were screened microbiologically by microscopy and culture of swabs (ear, nose, endotracheal tube, umbilicus) and fluid (blood, cerebrospinal fluid, urine, and gastric aspirate). Infection was considered proved in babies who had positive blood or cerebrospinal fluid cultures or +++ cultures with pure growth of a single organism from urine or more than one swab site. The performance of putative predictors of infection (clinical/laboratory criteria, C reactive protein, platelet count, and complement activation markers) could then be compared with microbiological screening, used in this study to define the true disease state. Measurement of complement activation and C reactive protein was carried out by investigators who were unaware of clinical details.

SUBJECTS

Fifty six babies (28 boys, 28 girls) with a median gestational age of 33 weeks (range 25–40), median age at time of study 1 day (range 1–73) and median birth weight 1700 g (range 434–4180) who were admitted to the neonatal intensive care unit of King's College Hospital were studied.

Forty two babies with clinically suspected infection were screened microbiologically. In 17 babies, sepsis was proved, the causative organisms being: *Staphylococcus epidermidis* (n=6), group B streptococcus (n=3), *Streptococcus faecalis* (n=2), *Pseudomonas aeruginosa* (n=2), *Escherichia coli* (n=1), *Proteus mirabilis* (n=1), *Streptococcus viridans* (n=1), and bacteroides species (n=1). Fifteen of these babies had clinical/laboratory criteria indicating probable infection and two were classified as having possible infection.

Table 1 Clinical criteria used to diagnose infection in neonates

(1) Possible infection		
At least one of the following		
Prolonged rupture of membranes		Maternal fever
Gram strain positive in gastric aspirate		Fever (37·5–38°C)
Meconium staining		Vomiting
Increased gastric aspirate		Mild abdominal distension
(2) Probable infection		
One each of the following clinical *and* laboratory criteria		
(a) Clinical		
Lethargy		Apnoea
Poor spontaneous movement		Temperature instability
Bradycardia		Hypotension
Cyanosis		Grunting
Diarrhoea		Haematochezia
Severe abdominal distension/tenderness		Sclerema neonatorum
Petechiae		
(b) Laboratory		
	First 48 hours	*After 48 hours*
White cell count ($\times 10^9/l$)	<3	>24
Neutrophil count ($\times 10^9/l$)	<2·5	2·5< >7·5

Fourteen babies had no suspicion of infection, and these formed the control group (seven boys, seven girls) with a median gestational age of 34 weeks (range 26–40), median age at time of study 1 day (range 1–73), and median birth weight 1580 g (range 840–4180). There were no significant differences in gestation, age, or birth weight between controls and babies with suspected infection, irrespective of whether the microbiological screen was positive or not.

Blood collected in a final concentration of edetic acid of 10 mmol/l and remaining after routine haematological tests had been performed (0·5–1 ml) was centrifuged at 1000 *g* at 4°C for 15 minutes and the plasma was stored at −70°C. When there was insufficient plasma for all parameters to be measured, analyses were performed in the following order of priority: C reactive protein, Ba, C3d, and C4d.

C4d, Ba, AND C3d MEASUREMENT

C4d concentrations were determined by a nephelometric technique.[16] Briefly, plasma was brought to 11% final concentration of polyethylene glycol 6000 (PEG) (Sigma Chemicals) and centrifuged at 1500*g* for 30 minutes at 4°C. This manoeuvre precipitates C4 and its larger fragments, leaving C4d in the supernatant. The concentration of C4d was then measured by laser nephelometry, using anti-C4 intact antiserum (Behring Diagnostics). Ba and C3d plasma concentrations were measured using similar techniques and antifactor B and anti-C3d antiserum (Dakopatts) after treatment of the plasma samples with high PEG concentrations.[15 18] C4d and C3d results were expressed as percentages of 100% C3d and C4d standards, obtained by exhaustively activating complement through the classical pathway by incubating normal human serum with heat aggregated immunoglobulin. Ba results were expressed as percentages of 100% Ba standard, obtained by exhaustively activating the alternative complement pathway by incubation of normal human serum with inulin.

C REACTIVE PROTEIN MEASUREMENT

Plasma concentrations of C reactive protein were measured using a commercially available kit (Behring Diagnostics). Latex particles coated with anti-C reactive protein antiserum are aggregated by serum C reactive protein and the light scatter measured by nephelometry. Results were expressed in mg/l.

STATISTICAL ANALYSIS

Values of the complement indices, C reactive protein, white cell, neutrophil, and platelet counts, gestational age, and birth weight in each test group conformed to a normal distribution according to the Kolmogorov-Smirnov goodness of fit test and were compared using one way analysis of variance (ANOVA) and multiple Student's *t* tests. Statistical computations were performed using the Statistical Package for the Social Sciences (SPSS-X) of the University of London Computer Centre Amdahl 5980/300. Frequency distributions

Table 2 Means (SD) and their statistical comparison in subjects with suspected infection (possible or probable) and controls

	(1) Controls	Babies with suspected infection		ANOVA (F ratio)	Student's t tests (t value)			
		(2) Possible	(3) Probable		(1) v (2)	(2) v (3)	(1) v (3)	(1) v (2 and 3)
C4d (%)	22·0 (9·9)	16·5 (8·5)	32·0 (17·4)	4·36*	1·19†	−2·75*	−1·34†	−0·60†
(n)	(6)	(10)	(17)					
Ba (%)	63·5 (27·8)	48·5 (22·9)	120·3 (71·3)	12·03***	1·68†	−4·35***	−2·61*	−1·02†
(n)	(12)	(21)	(19)					
C3d (%)	23·6 (8·6)	20·8 (4·9)	31·9 (8·9)	10·85***	1·11†	−4·75***	−2·42*	−0·83†
(n)	(9)	(19)	(18)					
C reactive protein (mg/l)	16·8 (15·5)	38·8 (46·8)	47·7 (46·3)	2·37†	−1·69†	−0·61†	−2·39*	−2·07*
(n)	(14)	(22)	(20)					
Platelet count (×10⁹/l)	320 (78)	267 (106)	223 (105)	2·63†	1·29†	1·19†	2·39*	1·91†
(n)	(14)	(22)	(20)					

†=Not significant.
*p<0·05, **p<0·01, ***p<0·001.

were analysed using the χ^2 test with Yates's correction for small numbers and similar levels of significance were obtained using Fisher's exact probability test.

Results

COMPLEMENT MEASUREMENTS

When all babies with suspected infection were considered as a whole, concentrations of C4d, Ba, and C3d were similar to those of controls (table 2). In babies in whom infection was only considered possible, concentrations of these complement activation products were also similar to those of controls. Babies with clinical/laboratory criteria indicating probable infection had C4d concentrations similar to those of controls, but significantly higher concentrations of Ba and C3d. Babies with probable infection had concentrations of C4d, Ba, and C3d that were significantly higher than those in babies with possible infection.

Babies with suspected infection but negative microbiological screens had concentrations of C4d, Ba, and C3d similar to those of controls (table 3, fig 2). In contrast, Ba and C3d were significantly higher in babies with proved infection when compared with controls, though C4d concentrations were similar in the two groups. Concentrations of C4d, Ba, and C3d were significantly higher in patients with proved infection than in those with suspected infection but with negative microbiological screens. There was no relationship between the type of organism, whether Gram positive or negative, and the concentrations of any of the complement fragments.

To assess the relationship between the frequency of high concentrations of complement fragments and the outcome of microbiological screening in babies with suspected infection, mean concentrations in the sera from the controls + 2SD were used as the upper limit of normal. Concentrations of Ba greater than the mean for controls + 2SD were found in eight of 17 neonates with proved infection and two out of 25 in whom microbiological screen was negative (χ^2=6·81; p<0·01). High concentrations of C4d were found in four out of 17 neonates with proved infection but in none of the 25 with negative sepsis screens (χ^2=3·42; p>0·05). High concentrations of C3d were found in two out of 17 babies with proved infection and one neonate with a negative sepsis screen (χ^2=0·11; p>0·05).

C REACTIVE PROTEIN

When all babies with suspected infection were considered as a whole, concentrations of C reactive protein were significantly higher than controls (table 2). In those considered to have only possible infection, C reactive protein was higher than in controls but the difference did not reach statistical significance (p=0·10). Babies with clinical/laboratory criteria indicative of probable infection had C reactive protein concentrations significantly higher than controls. Concentrations of C reactive protein were similar in babies considered to have possible infection and those with probable infection.

Babies with suspected infection but whose microbiological screening tests were negative had significantly higher C reactive protein than controls (table 3, fig 2) and higher concentrations than babies with microbiologically proved infection, though this was not statistically significant (p=0·44). Babies with proved

Table 3 Means (SD) and their statistical comparison in subjects with suspected infection (proved microbiologically or not) and controls

	(1) Controls	Babies with suspected infection and microbiological screen		ANOVA (F ratio)	Student's t tests (t value)		
		(2) Negative	(3) Positive		(1) v (2)	(2) v (3)	(1) v (3)
C4d (%)	22·0 (9·9)	18·[illegible] (9·4)	36·1 (17·8)	6·84**	−0·85†	−3·49**	−1·80†
(n)	(6)	(14)	(13)				
Ba (%)	68·5 (27·8)	48·2 (26·9)	134·1 (66·9)	19·69***	1·59†	−5·67***	−3·43**
(n)	(12)	(24)	(16)				
C3d (%)	23·6 (8·6)	21·[illegible] (7·0)	31·9 (8·4)	7·93**	0·58†	−3·97***	−2·45*
(n)	(9)	(21)	(16)				
C reactive protein (mg/l)	16·8 (15·5)	47·[illegible] (48·7)	36·2 (42·7)	2·53†	−2·29*	−0·78†	−1·61†
(n)	(14)	(25)	(17)				
Platelet count (×10⁹/l)	320 (78)	245 (111)	245 (103)	1·78†	1·74†	0·06†	1·82†
(n)	(14)	(25)	(17)				

†=Not significant
*p<0·05, **p<0·01, ***p<0·001

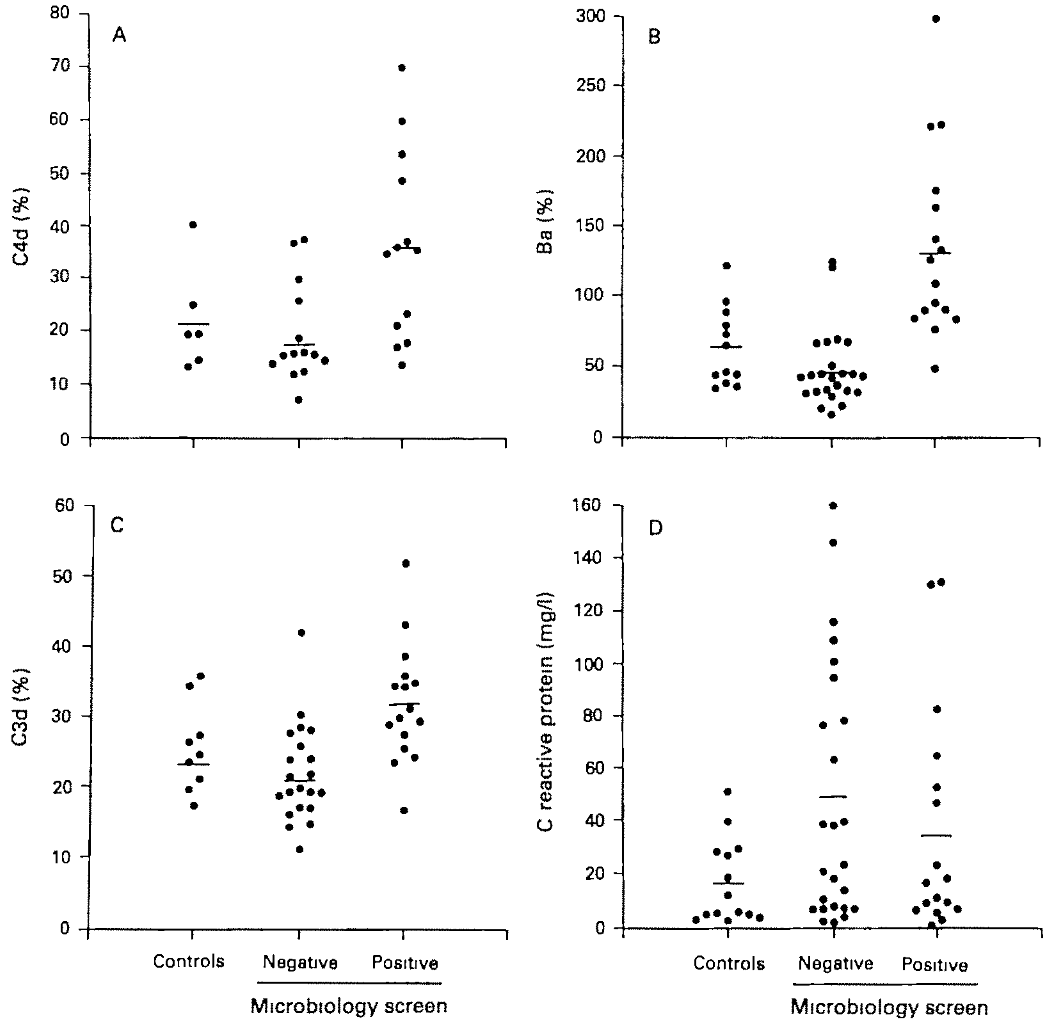

Figure 2 Concentrations of the complement fragments (A) C4d; (B) Ba, (C) C3d, and (D) C reactive protein in control babies and neonates with suspected infection divided according to the outcome of microbiological tests.

infection had higher concentrations of C reactive protein than controls, though not significantly so (p=0·12).

Concentrations of C reactive protein greater than the mean of the controls + 2SD were found in five of 17 neonates with proved infection and in nine out of 25 in whom the microbiological screening tests were negative (χ^2=0·01; p>0·05).

HAEMATOLOGICAL MEASUREMENTS

In all babies with suspected infection considered as a whole and those who were considered only to have possible infection, white cell, neutrophil, and platelet counts were not statistically different from those of the controls. Babies with clinical/laboratory criteria indicative of probable infection had platelet counts significantly lower than those of the controls but the counts were similar to those in babies in whom infection was only considered possible.

The white cell, neutrophil, and platelet counts were not statistically different in babies with microbiologically proved infection compared with those in babies with suspected infection whose microbiological screening tests were negative and those of controls.

Using previously established criteria for the definition of abnormal white cell (<5·0 or >20·0×10^9/l),[5] neutrophil (<2·0 or >7·5×10^9/l),[11] and platelet counts (<150×10^9/l)[7] there were no significant relationships between abnormal values of these and the outcome of microbiological screening tests in babies with suspected infection (χ^2=0·02, 0·08, and 0·04, respectively).

PERFORMANCE CHARACTERISTICS OF LABORATORY INDICATORS OF NEONATAL INFECTION

The sensitivity and specificity of the laboratory indicators C4d, C3d, Ba, C reactive protein, and white cell, neutrophil, and platelet counts in predicting infection are shown in table 4, using microbiologically proved infection as the reference disease state. The values of each parameter that are considered abnormal are those described above. The three markers of complement activation had the highest specificity of any laboratory index, and Ba provided the most sensitive marker of infection. When a high value of any of the three complement fragments was used as the criterion for prediction of infection, no improvement in performance was obtained (sensitivity 52·9%, specificity 88·0%).

Discussion

The diagnosis of infection presents one of the most difficult problems in the care of preterm babies. Current clinical and haematological diagnostic criteria, while identifying babies

Table 4 Performance characteristics of laboratory indicators of neonatal infection

Indicator	*% Sensitivity**	*% Specificity†*
C4d	30·7	100·0
Ba	47·1	92·0
C3d	12·5	95·2
C reactive protein	29·4	64·0
White cell count	17·6	76·2
Platelet count	5·9	84·2
Neutrophil count	29·4	63·2

*Measurement of how well the presence of infection was predicted
†Measurement of how well the absence of infection was predicted

who are eventually proved to be infected, inevitably include many who are not, yet they all undergo intensive chemotherapy. Many studies have been performed to sharpen the criteria, employing other individual or groups of tests, but with only limited success.[4-7] The present study was initiated to investigate the usefulness of measuring indices of complement activation in diagnosing neonatal infection. As complement forms an important arm of the innate immune system, it provides protection against infection during the neonatal period, when the specific, acquired immune system is still relatively immature.[18] The concentrations of fragments C4d, Ba and C3d, which are released after cleavage of their parent molecules C4, factor B and C3, provide both unequivocal evidence, and a measurement, of complement activation proceeding through the classical, alternative, and common pathways.[19] It follows that their concentrations may reflect infectious episodes in the neonate and be of use in the early diagnosis of sepsis.

In the present study, neonates with a presumptive diagnosis of infection made on conventional clinical and haematological grounds had no significant increase in concentrations of complement fragments. However, when the diagnosis was made using an accepted reference test, namely the culture and identification of organisms from relevant sites, high concentrations of Ba and C3d were present in the infected group, indicating an increase in activation through the alternative and common pathways, but normal concentrations were found in the group with negative cultures. Moreover, concentrations of C4d, Ba, and C3d were higher in babies with positive than in those with negative cultures. High levels of complement activation, therefore, may be able to identify infected neonates in whom a diagnosis of possible sepsis is made.

By comparison, other widely accepted markers of infection, such as C reactive protein[8-10] and the platelet count,[7] failed to discriminate between infected and non-infected neonates. In our study, C reactive protein was the only parameter which was higher in neonates with any suspicion of infection, whether possible or probable. At first sight, this finding lends apparent support to the concept that C reactive protein may be useful in managing the neonate with suspected sepsis. Further examination shows, however, that concentrations of C reactive protein were not statistically different from controls in babies from whom organisms were cultured, while in babies with negative infective screens C reactive protein was higher than in controls. These results question the use of C reactive protein as a marker of neonatal infection. They suggest that its popularity rests largely on its tendency to confirm the clinician's suspicion, rather than its ability accurately to identify infected neonates.

The explanation for complement activation in infected babies could be the presence of preformed, maternal antibodies directed against micro-organisms. The antibodies that cross the placenta belong to the IgG isotype, and are efficient activators of the complement system.[14] Activation could also take place after direct triggering of the alternative pathway by the lipopolysaccharide cell walls of bacteria.[20] The fact that evidence of complement activation is found in infected babies is not surprising, therefore, and it provides a potential tool with which to identify this population.

This is the first study to demonstrate that high values of indices of complement activation are found in neonates with microbiologically proved infection. The relative performances of complement activation indices, C reactive protein and white cell, neutrophil, and platelet counts are reflected in the sensitivity and specificity with which they were capable of predicting culture proved infection. C reactive protein and haematological counts lack the performance characteristics required of a useful laboratory marker of neonatal infection. Fragment Ba, on the other hand, has a combination of high specificity and reasonable sensitivity in the prediction of culture positive infectious episodes in the neonatal period. As complement activation products can be measured within hours, as opposed to the 24–48 hours required for blood, fluid and swab cultures, fragment Ba could offer the clinician an early marker, providing a much needed adjunct to the clinical diagnosis of infection in neonatal intensive care.

Mark Peakman is a Wellcome Trust Research Training Fellow.

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Archives of Disease in Childhood 1992; 67. 808–812

Receiver operating characteristic curves for comparison of serial neutrophil band forms and C reactive protein in neonates at risk of infection

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Abstract

The performance of indirect indices of infection in the newborn vary because of differences in techniques, including diagnostic cut off levels. We have compared serial neutrophil band cell counts with C reactive protein measured by rate nephelometry. The 'gold standard' was a positive culture and the performance of the tests was compared by the technique of receiver operating characteristics (ROC) as well as sensitivity and specificity.

A total of 172 septic screens were performed in 56 patients. The operational diagnostic cut off values were: C reactive protein >3 mg/l, immature:total neutrophil ratio (I:T ratio) >0·2, and band count >5% Compared with the sensitivity of C reactive protein (71%), I:T ratio (34%) was significantly different but band count (69%) was not. The specificity of C reactive protein (72%) was better than band count (39%) but no better than I:T ratio (73%). ROC curves were constructed for all possible diagnostic cut off values of the tests and superior performance was demonstrated for C reactive protein compared with band count and I:T ratio.

We conclude that C reactive protein is a useful early indicator of infection in neonates and that ROC curves permit comprehensive and graphic comparison between tests and the calculation of optimal diagnostic cut off values.

Early clinical diagnosis of neonatal infection is difficult because of the non-specific presentation of infection, and a delay in diagnosis may be associated with increased morbidity and mortality. Early laboratory indicators of infection are therefore required to facilitate early diagnosis.[1-10] Infection activates the acute phase response which may be detected by alterations in the peripheral blood neutrophils[1-3] and an increase in serum proteins such as C reactive protein.[5] Although such changes are non-specific, they are thought to give indirect evidence of infection.[3-8]

Single determination of neutrophil band forms and other indices of infection has been used for early diagnosis of infection while the results of blood cultures are awaited,[3,5-7,10] but wide variation exists in the reported performance of these tests. Combinations of tests have been used to improve the test performance of single determinations,[5,10,11] while serial determination of C reactive protein has also been utilised to improve sensitivity by detecting changes in C reactive protein rather than specific diagnostic cut off points.[12] Serial C reactive protein has also been used for monitoring of antibiotic treatment and to detect early recurrence of infection.[13,14]

Standard non-parametric statistical comparisons of test performances such as χ^2 and McNemar tests may be complemented by the calculation of receiver operating characteristics (ROC),[15] permitting direct comparison of tests over *all* diagnostic cut offs. We have therefore used this technique as well as standard statistical methods to compare the performance of paired serial C reactive protein concentrations and neutrophil band counts in neonates with suspected infection.

Subjects and method

All babies admitted to the unit for either suspected infection or management of prematurity, low birth weight, respiratory distress syndrome, and asphyxia neonatorum were studied over a three month period. Daily samples of 0·5 ml of blood, collected in EDTA, were drawn from arterial/umbilical arterial lines or from capillary blood for routine full blood count. This sample was used for the differential count including band forms and the remaining plasma was used for determination of C reactive protein. A septic screen (culture of blood, cerebrospinal fluid, urine, and endotracheal secretions) was performed when indicated and processed according to standard microbiological procedures. Infection was suspected on the basis of at least one of the following criteria. (1) Clinical indication: including prolonged rupture of membranes, respiratory distress syndrome, outborn, apnoea, lethargy, irritability, temperature instability, non-specific abdominal distension, and unexplained metabolic acidosis. (2) Neutrophil band count of >5% of total white cell count (approximately equivalent to immature neutrophil:total neutrophil (I:T) ratio of 0·11 (95% confidence interval 0·07 to 0·15, unpublished data). (3) C reactive protein concentration of >8 mg/l. These values constitute the operational diagnostic cut off values for the tests, above which the test is considered positive for infection. The clinician responsible for the care of the patient at the time of suspected infection determined the need for culture and treatment.

C reactive protein was measured by rate nephelometry using a Beckman Array System

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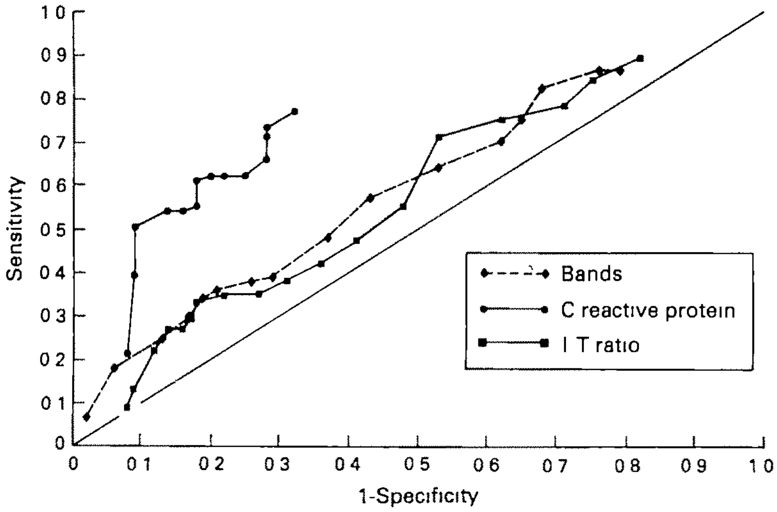
Accepted 20 February 1992

protein analyser (Beckman Instruments, C reactive protein reagent kit 449760). An aliquot of 50 µl plasma was diluted with 250 µl of Beckman buffer and centrifuged to remove immune complexes and limit turbidometric interference. The lower detection limit used was 6 mg/l because of increased interference from other proteins below concentrations of 4–6 mg/l. The within-run coefficient of variation of the test was 3–5% and between-run coefficient of variation was <5%. The Beckman assay has been compared with electroimmunodiffusion and radial immunodiffusion assays and correlation coefficients of 0·986 and 0·993 respectively were obtained.[16]

Blood counts were estimated by Coulter counter in the routine paediatric haematology laboratory and neutrophil band counts were determined by duty technicians in accordance with accepted criteria for the detection of band forms,[5] but neutrophil precursors before band forms were recorded separately.

When considering the study size a false positive rate of 60% for band forms was estimated and a 50% reduction in false positives was considered clinically worthwhile. Forty nine pairs of C reactive protein concentrations and band counts were required to detect such a difference at the 0·05 level of significance (two sided) and with 90% confidence.[17] Three methods of comparison of test performance were used. (1) Comparison of the binomial proportions (sensitivity, specificity, and positive predictive accuracy) was by the χ^2 test with Yates's continuity corrrection and (2) the McNemar test was used to compare the ability of the test to predict the culture result. These two methods compared the tests at single diagnostic cut off levels. (3) ROC of the infection indices.[15] This technique allows a comparison to be made of a test's ability to discriminate between two populations regardless of diagnostic cut off levels selected. The ROC curve is constructed by plotting the test sensitivity (equivalent to the true positive rate) on the y axis and 1-specificity (equivalent to the false positive rate) on the x axis, for all possible cut off values of the diagnostic test (see figure). The diagonal line represents a test that produces false positive results (x axis) at the same rate as true positive results (y axis). A good diagnostic test would be represented by a ROC curve in the upper left hand triangle as close as possible to the 'north west' corner.



ROC curves of infection indices. 1-Specificity is equal to the false positive rate

Table 1 Patient details

No of patients	56
Median gestation (weeks)	31
Range	25–40
Median birth weight (g)	1448
Range	693–3862
M:F	33:23
No with respiratory distress syndrome	
On IPPV*	43
On oxygen	7
No on total parenteral nutrition	43
No of deaths	7
Median day of screen	13
Range	1–131
Median No of screens	5
Range	1–11

*IPPV=intermittent positive pressure ventilation

Results

A total of 172 septic screens were performed on 56 patients. The median gestational age (range) of the 56 patients was 31 weeks (25–40) and median weight (range) 1448 g (693–3862). Details of the patients are shown in table 1.

Cultures were taken between one and 11 times (median 5) from each patient. Of the 172 cultures, 28 were performed on admission on day 1 and of these 2/28 (7%) were positive (one *Escherichia coli* and one *Staphylococcus epidermidis*). Fifty four (37·5%) of the remaining 144 cultures were positive giving an overall positive culture rate of 56/172 (32·5%). The frequency of organisms cultured is shown in table 2 and the infection indices of positive cultures are shown in table 3.

The culture result was regarded as the 'gold standard' against which to compare the performance of the acute phase indices. The sensitivity (proportion of positive cultures detected by the test), specificity (proportion of negative cultures correctly identified by the test), and efficiency (proportion of all culture results correctly determined by the test – that is, the sum of sensitivity and specificity[18]), were calculated. C reactive protein had a sensitivity of 71·4% and specificity of 72·4% as compared with percentage band count with sensitivity of 69·6% and specificity of 38·8%. The sensitivity of the I:T ratio was 34% and specificity of 73%.

Table 2 Culture results

Organism	*No of cultures*
Staphylococcus epidermidis	41
Staphylococcus aureus	4
Escherichia coli	2
Klebsiella pneumoniae	2
Pseudomonas aeruginosa	1
α Haemolytic streptococcus	1
Bacillus species	1
Neisseria meningitidis	1
Candida albicans	3
Total No of positive cultures	56
Total No of negative cultures	116
Total No of cultures	172

Table 3 Acute phase indices for positive cultures (n=56)

Organism	*Initial C reactive protein (mg/l)*	*Peak C reactive protein (mg/l)*	*Band count*	*I·T ratio*
α Haemolytic streptococcus	30	62	9	0·16
Staphylococcus aureus	14	60	21	—
Staphylococcus epidermidis	31	31	7	0·12
Staphylococcus epidermidis	75	84	7	0·10
Escherichia coli	7	82	31	0·57
Klebsiella species	251	251	14	0·65
Staphylococcus epidermidis	6	6	8	0·14
Staphylococcus epidermidis	6	43	8	0·15
Staphylococcus epidermidis	6	30	1	0·01
Staphylococcus aureus	136	227	20	0·40
*Neisseria meningitidis**	88	120	35	3·18
Escherichia coli	8	115	26	1·18
Staphylococcus epidermidis	18	58	9	0·12
Staphylococcus epidermidis	39	92	15	0·23
Pseudomonas aeruginosa	13	181	4	0·17
Staphylococcus epidermidis	22	84	9	0·11
Staphylococcus epidermidis	14	115	13	0·20
Staphylococcus epidermidis	23	66	4	0·04
Staphylococcus epidermidis	39	70	27	0·41
Staphylococcus epidermidis	70	70	0	0·00
Staphylococcus epidermidis	107	119	0	0·00
Staphylococcus epidermidis	6	6	0	0·00
Staphylococcus epidermidis	6	6	17	0·38
Staphylococcus epidermidis	50	91	9	0·11
Staphylococcus epidermidis	8	66	5	0·07
Staphylococcus epidermidis	10	10	6	0·12
Candida albicans	32	44	26	0·49
Staphylococcus epidermidis	35	53	33	0·82
Staphylococcus aureus	27	92	24	0·46
Staphylococcus epidermidis	9	12	8	0·12
Staphylococcus epidermidis	79	79	16	0·26
Staphylococcus epidermidis	6	6	54	3·18
Bacillus species	6	60	17	0·34
Candida albicans	65	93	11	0·18
Staphylococcus epidermidis	26	54	5	0·07
Staphylococcus epidermidis	42	42	5	0·05
Staphylococcus epidermidis	7	12	6	0·10
Staphylococcus epidermidis	19	62	14	0·30
Staphylococcus epidermidis	6	—	1	0·04
Staphylococcus epidermidis	9	10	1	0·02
Staphylococcus epidermidis	14	145	0	0·00
Staphylococcus epidermidis	175	190	7	0·12
Staphylococcus epidermidis	6	6	5	0·16
Staphylococcus epidermidis	6	6	3	0·04
Staphylococcus epidermidis	6	6	8	0·11
Candida albicans	32	112	15	0·26
Staphylococcus epidermidis	24	27	7	0·10
Staphylococcus epidermidis	45	45	9	0·16
Staphylococcus epidermidis	6	5	4	0·11
Staphylococcus epidermidis	6	5	1	0·02
Staphylococcus epidermidis	175	190	7	0·12
Staphylococcus epidermidis	10	43	10	0·24
Staphylococcus epidermidis	15	15	6	0·12
Staphylococcus epidermidis	143	148	8	0·12
Staphylococcus epidermidis	39	70	27	0·41
Staphylococcus aureus	61	116	21	0.52

*In the cerebrospinal fluid.

The performance characteristics are shown in table 4. As the tests were paired, the McNemar test was used to test the hypothesis that no difference existed between the ability of the tests to discriminate between infected and non-infected populations. C reactive protein was significantly different from both bands ($\chi^2=16\cdot7$, $p<0\cdot0001$) and I:T ratio ($\chi^2=5\cdot8$, $p<0\cdot05$). C reactive protein was more efficient than bands and I:T ratio in all three postnatal period divisions but this only achieved statistical significance ($p<0\cdot05$) when compared overall with neutrophil bands.

The ROC curves are shown in the figure. The C reactive protein curve is to the left of both bands and I:T ratio indicating superior performance at all cut off values. Statistical comparison at single points on the ROC curves of the tests was possible by χ^2 for paired samples by selecting arbitrary points on each curve with equivalent sensitivity. When a sensitivity point of 0·71 for C reactive protein was compared with the closest equivalent band count sensitivity of 0·70 a significant difference was present ($\chi^2=18\cdot55$, $p<0\cdot001$) and similarly for C reactive protein (0·71) and I:T ratio (0·71) ($\chi^2=10\cdot78$, $p<0\cdot01$). When equivalent false positive rates (1-specificity) were compared for C reactive protein (0·28) and bands (0·29) ($\chi^2=5\cdot31$, $p<0\cdot05$) and for C reactive protein (0·32) and I:T ratio (0·31) ($\chi^2=5\cdot014$, $p<0\cdot05$) significant differences existed confirming the superior performance of C reactive protein as implied by the position of the C reactive protein ROC curve. If a complete C reactive protein curve could have been plotted then the area under the curves could have been compared to quantitate statistically the performance of the test over the entire range of possible cut off values.

The median peak (range) concentration of C reactive protein was 62 mg/l (6–251) in the positive cultures overall and a median of 6 mg/l (6–139) in negative cultures. In the cultures that yielded *S epidermidis*, the peak C reactive protein was 44 (6–190) and in the other cultures a peak C reactive protein of 112 (44–251) was measured.

The effect on C reactive protein and band counts of events such as intraventricular haemorrhage, pneumothorax, intercostal drainage, and steroid administration was recorded. Of the five patients who had an intercostal drain insertion for pneumothorax, none had a recordable change in C reactive protein concentration. Sixteen patients had an intraventricular haemorrhage varying in severity from subependymal haemorrhage to intraventricular haemorrhage with associated parenchymal echodensity while daily C reactive protein was being measured. Only one

Table 4 Performance characteristics of acute phase indices at diagnostic cut off values: C reactive protein > 8mg/l, band >5%, and I:T ratio >0·2

Positive		*% Sensitivity*		*% Specificity*		*% Efficiency*		*Predictive accuracy (%)*
≤7 days	C reactive protein	55	(6/11)	88	(44/50)	82	(50/61)	50
	Bands	64	(7/11)	46*	(23/50)	49	(30/61)	21
	I:T ratio	55	(6/11)	24**	(35/50)	67	(41/61)	29
8–28 days	C reactive protein	68	(19/28)	72	(26/36)	70	(45/64)	66
	Bands	68	(19/28)	28*	(10/36)	45	(29/64)	41
	I:T ratio	33**	(9/27)	83	(30/36)	62	(39/63)	60
>28 days	C reactive protein	88	(15/17)	47	(14/30)	62	(29/47)	48
	Bands	76	(13/17)	40	(12/30)	53	(25/47)	42
	I:T ratio	24*	(4/17)	67	(20/30)	51	(24/47)	29
Overall	C reactive protein	71	(40/56)	72	(84/116)	72	(124/172)	56
	Bands	69	(39/56)	39*	(45/116)	49**	(84/172)	35**
	I·T ratio	34**	(19/55)	73	(85/116)	61	(104/171)	38
	Clinical	62	(35/56)	43*	(50/115)	50**	(85/171)	35**

Significant differences compared with C reactive protein in each postnatal age division. *=p<0,001, **p<0 05.

patient had a small increase in C reactive protein (11·2 mg/l) and another four had an increase but had concomitant infection. Four patients received dexamethasone with no change recorded in three but in one an increased C reactive protein was present because of infection which was being treated. Necrotising enterocolitis (intestinal pneumotosis and or perforation) occurred in three patients with a significant rise in C reactive protein. Two of three patients with transient abdominal distention of undetermined cause showed an increase in C reactive protein to 20–25 mg/l. Four patients had laparotomy and bowel resection for gastroschisis (n=2) and necrotising enterocolitis (n=2) and all had rapid and large increases in C reactive protein after surgery for up to five days. Daily intraventricular vancomycin by needle ventricular tap for the successful treatment of *S epidermidis* ventriculitis was associated with a steady decline in C reactive protein.

Discussion

There is a wide range of reported sensitivity and specificity for I:T ratio and C reactive protein due to variations in methods, study design, or the definition of infection.[3 7 10 11 19] Factors which may account for the reported variability of I:T ratio performance include: the I:T ratio is operator dependent, neutrophils are affected by non-infective events,[4] and I:T ratio is less sensitive after the first week of life.[20] Several factors may influence the performance of C reactive protein. First the timing of the sample in relation to the infection screen. Second, the measurement method used: quantitative measures have recently replaced semiquantitative methods.[12] Third, the concentration of C reactive protein regarded as diagnostic of infection varies between studies. Wassunna *et al*, using a sensitive solid phase ligand-banding radiometric immunoassay for C reactive protein, have established a normal range for cord blood and for the first 48 hours of life in preterm babies.[12] Infection was associated with large changes in C reactive protein within a range below the detection limit of most commercially available assays.

We have found the performance of serial C reactive protein (sensitivity 71% and specificity 72%) to be within the range reported by others.[5 10] Although there was not significant difference in sensitivity between C reactive protein and bands the specificity was significantly better for C reactive protein because the false positive rate was half that of the band count. The I:T ratio had a sensitivity of 34·5% and specificity of 73% which contrasts with 90% and 78% found by Philip and Hewitt[5] but is similar to the results of Kite *et al* who found a sensitivity of 29·4% and specificity of 81·5%.[10] The large difference in the I:T ratio sensitivity reported by Philip and Hewitt and our result is probably due to the difference in timing of the tests. Philip and Hewitt examined babies with suspected infection during the first seven days only, whereas our study involved babies of all ages. I:T ratio is not as accurate after the first week and our results do show a trend from a sensitivity of 55% in the first week to 24% after 28 days (table 4).

Using ROC, more comprehensive comparisons between laboratory test performance are possible.[15] Although a complete C reactive protein curve could not be constructed because no cut off values below 6 mg/l were determined, individual point comparisons were significantly different. The performance of C reactive protein as an index of infection is therefore superior to band and I:T ratio for any given diagnostic cut off level. This technique can be used to compare the performance of other quantitative tests.

The lack of response of C reactive protein to pneumothorax and intraventricular haemorrhage is similar to the report of Wassunna *et al*, who found no increase in C reactive protein after arterial catheterisation, endotracheal intubation, germinal matrix haemorrhage, or intraventricular haemorrhage.[12] The difference in response between bands (and I:T ratio) and C reactive protein when babies received dexamethasone is of interest and likely to be of clinical relevance. The rapid rise in all forms of polymorphonuclear leucocytes makes bands and I:T ratio invalid for the detection of infection during steroid therapy. C reactive protein did not rise during steroid treatment but in our study it was not possible to determine changes in C reactive protein concentration in the range below our detection limit (6 mg/l).

Although the specificity of clinical assessment was only 43%, two episodes of *E coli* septicaemia, which were not detected by the acute phase indicators (C reactive protein failed in one and bands in the other), were suspected by the rapid onset of clinical signs. In both cases, C reactive protein and bands showed an increase when measured soon after clinical signs were evident. The doubling time of C reactive protein is 4–6 hours and a more sensitive C reactive protein assay may have given an earlier warning of infection by demonstrating a rise in C reactive protein before reaching the level of our current assay detection limit. (Using a more sensitive technique and analysing daily samples retrospectively, we have recently observed a rise in C reactive protein occurring below the previous detection limit of 6 mg/l for 24–48 hours before infection was suspected.)

In neonatal units C reactive protein is therefore an adjunct to good clinical assessment,[12] but the development of a rapid and sensitive detection method is needed to exploit the potential of C reactive protein as an early marker of infection. (Our current assay takes a total of 45 minutes of laboratory time for an average of 20 samples from the neonatal unit.) Appropriate gestation and postnatal age specific normal ranges could be used to evaluate changes in C reactive protein over time in patients where there is clinical uncertainty. Changes in serial C reactive protein concentrations in babies at high risk of infection can provide early evidence of infection, or confirm other non-specific infection indicators such as mild metabolic acidosis. However, a decision not to start antibiotics when clinically indicated cannot be based solely on a negative infection index, no matter how reliable the test. The advantage of serial quantitative C reactive protein tests are their objectivity and ready availability and this contrasts with the subjectivity of immature neutrophil estimations.

We conclude that *serial* C reactive protein estimation is significantly better than I:T ratio and percentage band count in detecting infection in preterm neonates. We plan to improve the detection limit for C reactive protein to be able to detect earlier changes in preterm infants at high risk of infection and to allow construction of complete C reactive protein ROC curves permitting more comprehensive comparisons with other tests. Using the ROC curve constructed with our current data we have determined an improved overall diagnostic cut off concentration of 7 mg/l to achieve a sensitivity of 75% (95% confidence interval 61 to 85%), specificity of 71% (59 to 83%) and a positive predictive accuracy of 55%.

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Archives of Disease in Childhood 1992; 67 813–817

Neutrophil chemotaxis and adhesion in preterm babies

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Accepted 13 December 1991

Abstract

To investigate the increased susceptibility to infection of very immature preterm neonates, neutrophil chemotaxis, Mac-1 adhesion receptor expression, and adherence to human umbilical vein endothelial cell monolayers (HUVE) were examined in neonates born at $\leq$32 weeks' gestation.

Chemotaxis of neutrophils from well preterm neonates towards casein or zymosan activated serum (ZAS) was reduced (mean SE) being for casein 88·6 (3·8) μm; ZAS 76·2 (4·3) μm compared with adults (casein 117·8 (1·4) μm; ZAS 112·1 (1·4) μm), but similar to term neonate neutrophils (casein 92·7 (4·5) μm; ZAS 75·9 (3·1) μm). Stimulated Mac-1 expression showed a similar pattern: reduced on preterm neutrophils compared with adults, but similar to term neonates. Preterm and term neonate neutrophils were both hyperadherent to HUVE when unstimulated, but showed an equally impaired ability to increase adhesion following stimulation. Casein stimulated chemotaxis and stimulated Mac-1 expression 'matured' towards adult levels of performance four weeks after preterm birth.

The increased incidence of sepsis in immature preterm infants is not due to greater defects of neutrophil migration.

The incidence of severe neonatal sepsis is greatly increased in very immature preterm neonates born weighing less than 1500 g.[1 2] The immune system is still immature at the time of fullterm birth and the deficiencies in humoural and cellular immunity are even more appreciable in the very immature preterm infant.[3]

Neutrophil polymorphonuclear leucocytes provide the major defence against bacterial invasion. The neutrophil dysfunction of term infants has been explored in numerous studies[4] but there has been little work on the functional capacity of neutrophils from very immature preterm infants, or the changes that occur after preterm birth.

Neutrophils respond to the stimulus of bacterial invasion by upregulating adhesion receptors on the cell surface, increasing adherence to the adjacent capillary endothelium, and migrating from the circulation to localise at the site of infection. The most important neutrophil adhesion receptor mediating stimulated adhesion and chemotaxis is the integrin Mac-1, defined by monoclonal antibodies (MoAb) to CD11b/CD18.[5]

Impaired neutrophil chemotaxis is a consistent finding in healthy term neonates.[6–12] This has been shown to be associated with impaired adherence to artificial surfaces[9–14] and a reduced ability to upregulate Mac-1 after cell stimulation.[15] Two previous studies of neonate neutrophil chemotaxis have included preterm infants,[11 16] but no previous study has investigated chemotaxis, Mac-1 expression, and adhesion in the group of immature preterm infants born before 32 weeks' gestation who are at the greatest risk of bacterial infection.

To examine further the increased susceptibility of preterm neonates to bacterial sepsis, we have measured chemotaxis and Mac-1 expression on neutrophils from well preterm infants born before 32 weeks' gestation and examined the changes that occur during early postnatal development. In addition, we have measured adhesion to endothelial monolayers as a more representative model of normal physiology than the reported adhesion assays using artificial surfaces.

Patients and methods

STUDY POPULATION

Twenty three 'well' preterm infants were studied soon after birth and at intervals during the first weeks of life. The median gestational age was 27 weeks (range 24–32) and median birth weight 1060 g (664–1952). Neonates were defined as 'well' if they had no evidence of infection and did not require mechanical ventilation for pulmonary insufficiency.

For analysis the infants were divided into groups: group 1, preterm neonates studied soon after birth at a median postnatal age of 1 day (range 1–4), n=22; group 2, preterm infants studied for a second time on median day 10 (5–21), n=23; group 3, preterm infants studied on median day 56 (28–70), n=10. For comparison, 28 healthy term neonates (group 4) were studied at the time of delivery by elective caesarean section, median gestational age 38 (38–40) weeks. All infants were studied in parallel with healthy adult controls (group 5), n=80.

The study was approved by and all blood sampling was in accordance with the Liverpool Maternity Hospital ethics committee guidelines.

ISOLATION OF NEUTROPHILS

Polymorphonuclear leucocytes from preterm neonates were isolated from umbilical arterial catheter or peripheral venous samples; from term neonates using cord blood collected at birth; and from adults by venepuncture. Blood was collected into heparin 10 U/ml and neutrophils separated on a sodium metrizoate/dextran gradient (Polyprep, Nycomed). Residual red cells were removed by hypotonic lysis and resuspended in Roswell Park Memorial Institute (RPMI) medium with calcium and magnesium (Flow Laboratories), the cell suspensions and all reagents being kept on ice. The purity of the neutrophil preparations was assessed by visual inspection of cytospin preparations. Viability, by trypan blue exclusion, was >95% in all cases.

PREPARATION OF REAGENTS

Stock solutions of f-Met-Leu-Phe (FMLP) (Sigma) were prepared in phosphate buffered saline (PBS). Casein (Sigma) was prepared as a 5% stock solution in PBS and before use diluted 1:10 in Hanks' BSS solution (Sigma). Zymosan activated serum (ZAS) was prepared by incubating zymosan (Sigma) with pooled fresh AB serum for 45 minutes at 37°C followed by 30 minutes at 56°C. Rose Bengal (Sigma) was prepared as a 0·25% solution in PBS; glutaraldehyde (BDH) as a 2% solution in PBS.

QUANTITATION OF MAC-1 RECEPTORS

Mac-1α chain (CD11b) was detected using MoAb Leu15 (Becton Dickinson); measurements were made on unstimulated neutrophils and after stimulation with 10^{-8}M FMLP for 15 minutes at 37°C. Cells were labelled for indirect immunofluorescence using saturating concentrations of MoAb and FITC goat anti-mouse IgG (Becton Dickinson). Surface stained cells were fixed in 1% paraformaldehyde and analysed on a Becton Dickinson FACS Analyser I. Forward and 90° light scatter were used to identify and isolate the neutrophil population for analysis. Fluorescence intensity distribution of 5000 cells was recorded on a three decade logarithmic scale and the mean fluorescence channel for each cell population calculated.

CHEMOTAXIS

Chemotaxis through a 3 µm pore size Millipore filter was measured in a modified Boyden chamber. Neutrophils, resuspended in Hanks' BSS with 1% bovine serum albumin were placed in the upper chamber and migrated towards casein or ZAS placed in the lower chamber After 90 minutes' incubation the leading front distance was measured on a calibrated microscope.

ADHESION TO HUMAN UMBILICAL VEIN ENDOTHELIAL CELLS

Conventional adhesion assays require large numbers of neutrophils. To allow adhesion to human umbilical vein endothelial cells (HUVE) to be assayed within the limits of the small cell numbers available from preterm infants, an assay system was developed using Rose Bengal staining.

HUVE cells were grown to a confluent monolayer in flat bottomed microtitre plate wells. Neutrophil suspensions in RPMI were adjusted to 5×10^6 cells/ml, warmed to 37°C, and 100 µl per well layered onto the HUVE with (stimulated) or without (unstimulated) 10^{-6} FMLP (final concentration). Each test suspension was added to four identical wells. To allow complete settling of the neutrophils onto the HUVE, the plate was incubated undisturbed for 15 minutes at 37°C before 100 µl of 2% glutaraldehyde solution was gently layered into each well to fix adherent neutrophils. Non-adherent neutrophils were removed by two washes with RPMI pipetted into the wells and removed by aspiration. Then 100 µl of 0·25% Rose Bengal was added to each well and incubated for 10 minutes after which any stain not absorbed into the cells was removed by four vigorous washes with PBS. To release absorbed stain from the cells into solution, ethanol (diluted 1:1 in PBS) was added to each well and incubated for 1·5 hours.

Optical density was measured at 570 nm in a Titertek Multiscan Plus microtitre plate reader, and the mean optical density of each set of quadruplicate wells taken. To quantify the number of adherent neutrophils the optical density of wells containing HUVE alone (mean of four) was subtracted from the optical density of each quadruplicate set of test wells.

Previous validation experiments had shown a linear relationship between the number of adherent neutrophils in a well and the optical density resulting from Rose Bengal staining.

Calculation of an adhesion index

This assay does not allow quantitation of the absolute number of adherent cells, and therefore results were related to the adherence of FMLP stimulated adult control cells (standard control), which was taken to represent an adhesion index of 100%. As the absolute number of adherent cells is related to the number of cells added to each well, all test and control neutrophil suspensions were adjusted to the same cell concentration. As an additional precaution, each test cell suspension was recounted at the time of dispensing into wells; these counts were used to make adjustment for any minor variation between cell number added to test wells and those added to control wells. The following formulas were used.

Adjusted optical density (OD)=

$$\begin{array}{c}\text{Measured OD adherent cells}\\ \text{(that is, OD test well–OD HUVE)}\end{array} \times \frac{\text{standard control cell count}}{\text{test cell count}}$$

then

$$\text{Adhesion index (\%)} = \frac{\text{adjusted OD test}}{\text{OD standard control}} \times 100$$

STATISTICAL ANALYSIS

Results are described by mean and standard error (SE). Study groups are compared by a two sample *t* test. Changes occurring within a single study population are additionally described by 95% confidence intervals (95% CI).

Analysis of neonatal neutrophil adhesion to HUVE monolayers is compared with the simultaneously tested adult controls by a paired *t* test because of the variation in performance between HUVE batches.

Results

Chemotaxis, Mac-1 (CD11b/CD18), and adherence to HUVE monolayers were measured sequentially in 23 clinically well preterm neonates born between 24 and 32 weeks' gestation. For comparison, 28 term neonates were studied at the time of birth.

CHEMOTAXIS

Random cell movement (chemokinesis) in all preterm neonate groups and in term infants was similar to adult controls (table). There was no statistically significant difference between groups.

Mac-1 expression and chemotaxis by study group. Values shown as mean (SE)

Study group (postnatal age)	*Fluorescence*		*Chemokinesis (µm)*	*Chemotaxis (µm)*	
	Mac-1R	*Mac-1S*		*Casein*	*ZAS*
(1) Well preterm (days 1–4)	15·4 (1 2)	72·5 (4·2)	42.9 (2·3)	88 6 (3·8)	76·2 (4 3)
(2) Well preterm (days 5–21)	15 6 (0·8)	75 2 (2·4)	42 3 (3·1)	91·7 (4 4)	81·2 (5·4)
(3) Well preterm (days 28–70)	13·9 (1·9)	110 2 (3·8)	41·3 (2 0)	104·0 (4·4)	80 6 (7·0)
(4) Term neonates (day 1)	18 5 (1·4)	85 7 (3·9)	41·6 (2 6)	92 7 (4·5)	75 9 (3·1)
(5) Adult	11 9 (0 3)	133 9 (2 3)	42·4 (1·2)	117·8 (1 4)	112·1 (1·4)

Mac-1R: Mac-1 expression on unstimulated neutrophils.
Mac-1S Mac-1 expression on neutrophils after stimulation with FMLP.

Directed migration (chemotaxis) was assessed in response to casein (fig 1, table) and ZAS (table). In response to either stimulus, the chemotaxis of neutrophils from well preterm neonates did not differ significantly from term neonates. However, leading front migration of both preterm and term neonate neutrophils was significantly reduced compared with simultaneously tested adult cells: $p<0·0001$ for group 1 *v* group 5, and for group 4 *v* group 5.

For preterm neonates tested at birth there was no correlation between chemotaxis and gestational age (casein $r=-0·234$; ZAS $r=-0·105$), or between chemotaxis and birth weight (casein $r=-0·142$; ZAS $r=-0·216$).

The preterm infants were studied again between the fifth and 21st postnatal day (group 2); all were well at the time of testing. Chemotactic responses were similar to those at birth (table). Postnatal maturation, represented by an increase in chemotactic response to casein, was observed in healthy infants after the fourth week following preterm birth (group 3) (fig 1, table): mean increase (group 1 *v* group 3)=15·4 µm; 95% CI 3·1 to 27·8; $p=0·02$. But cell migration remained impaired in comparison to adult neutrophils, $p=0·02$. Migration towards ZAS, however, did not increase significantly over a similar postnatal period: mean increase (group 1 *v* group 3)= 4·4 µm (95% CI–13·9 to 22·7). The difference in chemotaxis towards ZAS and casein in the postnatal period is unexplained, but may relate to differences in the clinical condition of the infants studied with each agent.

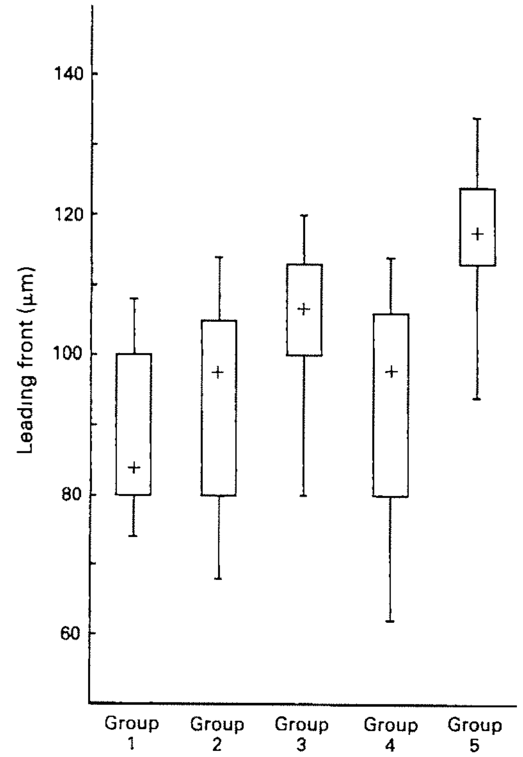

Figure 1 'Box plot', showing median and quartiles, of neutrophil chemotaxis (leading front distance) towards casein by study group. Group 1=well preterm days 1–4, group 2=well preterm days 5–21, group 3=well preterm days 28–70, group 4=term neonates (day 1), group 5=adults

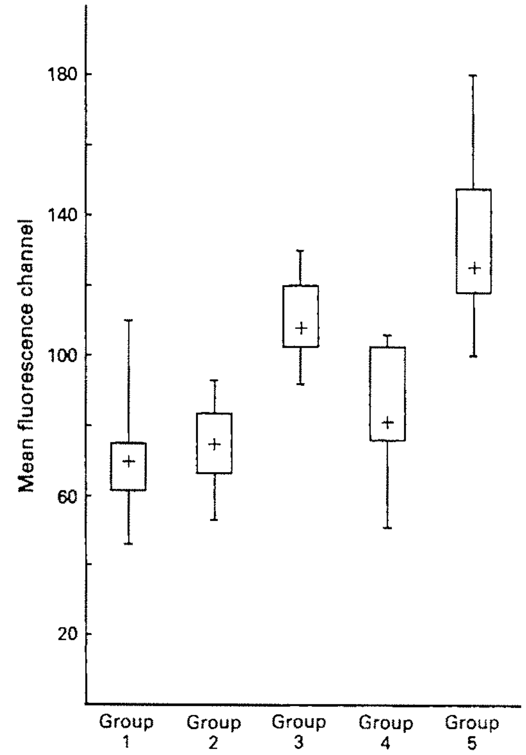

Figure 2 'Box plot' of Mac-1α expression on FMLP stimulated neutrophils by study group. Group 1=well preterm days 1–4, group 2=well preterm days 5–21, group 3=well preterm days 28–70, group 4=term neonates (day 1), group 5=adults.

MAC-1

The pattern of expression of Mac-1α chain (CD11b) on the neutrophil cell membrane after FMLP stimulation had some similarity with the observed chemotactic responses (fig 2). FMLP stimulated Mac-1α expression was significantly impaired in both healthy preterm neonates, and term neonates, compared with adult controls: p<0·0001 for group 1 *v* group 5, and group 4 *v* group 5 (table). Stimulated Mac-1α expression on preterm neutrophils was slightly less than on term neonate cells: p=0·03.

After preterm birth, the ability to upregulate Mac-1α improved in line with casein stimulated chemotaxis. After the fourth postnatal week (group 3) stimulated Mac-1α expression had significantly increased by a mean of 37·7 (95% CI 25·9 to 49·5); p<0·0001. However while Mac-1α expression by neutrophils from these older infants overlapped the adult range, the mean Mac-1α expression remained below the adult group mean (fig 2, table).

ADHESION TO HUVE

The adherence to unstimulated HUVE monolayers by unstimulated and stimulated neutrophils was examined in 16 term and seven well preterm neonates soon after birth (fig 3). Unstimulated neutrophils from both term and preterm neonates were hyperadherent compared with simultaneously tested adult control cells. The mean (SE) adhesion index of unstimulated term neonate neutrophils was 83·9 (6·5)% *v* adult neutrophils 56·6 (4·7)%, p=0·01; unstimulated preterm neutrophils, 69·7 (6·0)% *v* adults 46·9 (6·0)%, p=0·04. There was no significant difference between the adherence of unstimulated cells from term and preterm infants.

After FMLP stimulation, term neonate neutrophil adherence increased by a mean adhesion index of 25·6% (95% CI 16·1 to 35·1), and preterm neonate neutrophils by a mean of 20·1% (95% CI 6·8 to 33·5). Simultaneously tested adult controls increased adherence after FMLP stimulation by 43·4% (95% CI 33·4 to 53·4), and 53·1% (95% CI 38·5 to 67·8), respectively. Thus neutrophils from both term and preterm neonates exhibited significantly impaired upregulation of adherence in response to FMLP when compared with simultaneously tested adult cells, p=0·01 and p=0·002 respectively.

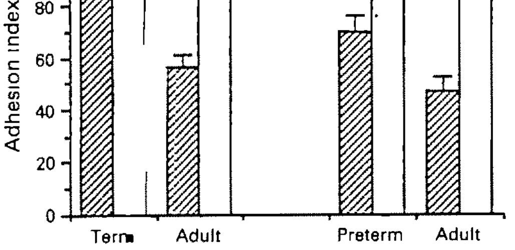

Figure 3 Bar chart showing mean (SE) adhesion index (%) to HUVE monolayers. The open bars represent FMLP stimulated neutrophil adhesion, cross hatched bars represent unstimulated adhesion. The 16 term infants are paired graphically with the simultaneously tested adult controls The seven well preterm infants are similarly paired with their own adult controls. The bars representing stimulated adult neutrophil adhesion have no error bar as the adhesion index is, by definition, 100% (see methods).

Discussion

This study has examined three aspects of neutrophil migration in healthy and stressed preterm neonates born between 24 and 32 weeks' gestation: expression of the Mac-1 (CD11b) component of the integrin adhesion complex (CD11/CD18), adhesion to a physiological substrate (HUVE monolayers), and chemotaxis.

Neutrophils from healthy preterm neonates uniformly displayed chemotactic responses and stimulated Mac-1 upregulation that were truncated compared with normal adults but which were no different from the responses of healthy fullterm neonates. After preterm birth casein stimulated chemotaxis and FMLP stimulated Mac-1 upregulation increased to approach adult levels after the fourth postnatal week.

These data support and extend the observations of others that neutrophil chemotactic ability is not related to gestational age. Krause *et al* studied four healthy newborn infants <1500 g[11] and Bektas *et al* 13 newborn infants of unspecified clinical status born between 28 and 36 weeks.[16] Both found that the preterm and term neonate neutrophils migrated equally towards ZAS.

The postnatal maturation of chemotactic ability after very premature birth has not previously been examined. Sacchi *et al* studied five infants born before 34 weeks and found delayed maturation of chemotaxis compared with four infants born between 34 and 36 weeks.[17] It was suggested that the delayed maturation may have been secondary to the increased number of infections in the more immature group. The same study found that a group of 10 term infants had established normal neutrophil chemotaxis by the time they and regained their birth weight. A more recently longitudinal study of healthy term neonates showed that normal adult levels of chemotaxis towards ZAS were established between 10 and 32 days after birth.[12]

In the present study of well preterm neonates born between 24 an 32 weeks' gestation, the postnatal increase in casein stimulated neutrophil migration was only slightly delayed in comparison to that reported for term infants. After the fourth week following preterm birth the chemotactic response of seven out of nine infants tested overlapped the adult range. Thus even in immature preterm neonates there is a rapid postnatal maturation of both chemotaxis and the ability to upregulate Mac-1, while these aspects of neutrophil function remain depressed and at a constant level throughout normal uterine development to term.

Likewise, neutrophils from preterm and term neonates behaved similarly in the adhesion assay, with a reduced ability to upregulate adherence compared with normal adult cells. It was not possible to do sequential postnatal studies of adherence in the preterm infants on account of the low number of circulating neutrophils in well infants after the first 10 postnatal days.[18]

Previous studies of neonate neutrophil adherence have examined adhesion to artificial surfaces, with variable results.[9-14 16] Only one study, by Anderson *et al*, has examined adherence to endothelium.[19] This study, which included term neonates only, agreed that their neutrophils had impaired upregulation of adherence when stimulated. However, in contrast to our finding that unstimulated neonate cells were hyperadherent, this published study reported reduced adherence to HUVE by unstimulated neonate cells. The difference may stem from differences in the adhesion assay techniques. In our assay adhesion to HUVE was measured at a time when adherence was maximal[20] by fixing the cell interactions at 15 minutes with glutaraldehyde. The longer neutrophil/HUVE interaction used by Anderson's group may mean that adhesion was measured after the hyperadherent phase had passed.[19 21]

The similar functional responses of neutrophils from term infants and preterm neonates born before 32 weeks' gestation suggests that the increased incidence of severe infection in immature preterm newborn infants is not related to differences in the ability of their neutrophils to adhere and migrate. The similarity between term and preterm neonate neutrophils suggests a state of arrested functional 'maturation' from at least 25 weeks' gestation in the developing fetus. The point in ontogeny at which neutrophils of the developing fetus reach this functional steady state, the mechanisms which maintain fetal neutrophil function in developmental limbo, and the changes that occur at birth to trigger the process of maturation are unknown.

We thank Professor R W I Cooke and Dr A M Weindling for permission to study infants under their care at the Liverpool Maternity Hospital. Thanks also go to Joyce Billington for additional technical assistance.

The study received financial support from Mersey Regional Health Authority.

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Archives of Disease in Childhood 1992; 67: 818–821

Serum erythropoietin concentrations in symptomatic infants during the anaemia of prematurity

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Abstract

A comparison was carried out between a series of neonates who weighed less than 1500 g at birth and received red cell transfusions for symptomatic anaemia of prematurity (group 1, $n=14$) and controls of similar gestational age and weight, who remained well and were not transfused during their nursery stay (group 2, $n=10$). Mean (SD) haemoglobin concentrations at birth were 163 (12) g/l and 183 (17) g/l ($p=0\cdot004$), respectively. Transfusion resulted in significantly better weight gain in six infants who had been growing poorly: mean (SE) 8·8 (2·8) g/day improved to 23·3 (2·1) g/day ($p<0\cdot002$). Geometric mean (SD) serum immunoreactive erythropoietin (SiEp) concentrations (17·7 (1·3) U/l) for the whole group of infants were similar to those of normal adults (17·4 (4·7) U/l) despite considerably reduced haemoglobin values. There was a significant inverse correlation between haemoglobin and log SiEp concentrations in the infants requiring transfusion ($r=-0\cdot43$; $p<0\cdot01$), but this was not apparent in the untransfused babies. Moreover, at haemoglobin concentrations below 120 g/l the mean (SE) SiEp concentration of 20 (1·08) U/l in group 1 was significantly higher than in group 2 (14 (1·06) U/l; $p=0\cdot002$). These data suggest that an increased concentration of SiEp early in the course of the anaemia of prematurity helps to identify those infants who would benefit from red cell transfusions, but that clinical criteria, although ill defined, do so equally well.

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Accepted 28 December 1991

Infants born prematurely experience an exaggerated fall in haemoglobin concentration compared with full term babies,[1] a significant proportion of them manifesting clinical features of anaemia,[2] where the common practice of transfusing red cells usually results in symptomatic improvement.

Recent studies have questioned the value and safety of such a practice in asymptomatic babies, particularly when based on packed cell volume figures alone.[3 4] Furthermore, as the criteria for red cell infusions in these individuals are largely clinical and ill defined, attempts have been made to find a laboratory investigation which might prove a reliable guide to justify this potentially hazardous intervention. It is known that the serum erythropoietin concentrations in preterm infants are inappropriately low for the degree of anaemia[5–8] when compared with adults with similar haemoglobin values, but that a physiological response to impaired tissue oxygenation will occur. Thus, increased concentrations of erythropoietin could identify infants who are hypoxic and who would be expected to benefit from additional red cells.

To test this postulate, serum immunoreactive erythropoietin (SiEp) concentrations in 14 infants transfused for symptomatic anaemia of prematurity were contrasted to 10 comparable babies who remained asymptomatic and untransfused throughout their nursery stay to establish whether the hormonal response differed in the two groups.

Patients and methods

Infants who were less than 34 weeks' gestation by Dubowitz score[9] and whose birth weights were under 1500 g were studied. Those with congenital or inherited disease, haemolysis, cardiac pathology, or who suffered acute blood loss were excluded. Infants were managed by the attending neonatal staff, who made all decisions about their day to day care, although transfusion was restricted to babies with signs attributable to anaemia and not for a low haemoglobin concentration alone. Transfusions comprised packed red cells in citrate-phosphate-dextrose-adenine 1 at a volume of 10 ml/kg of body mass. Folate, iron, and vitamin E were not given to any of the infants until the day before discharge.

Each infant was examined daily to document physical findings. Body weight, kilojoule intake, and all medical and supportive treatments were recorded until they were discharged at a weight of 2000 g.

The first blood count was performed 12 hours after birth and then at weekly intervals, using a standardised capillary microtechnique on the Coulter S Plus 2, together with a corrected reticulocyte count on 2000 cells. In patients who were transfused, 48 hours elapsed before sampling. Serum ferritin, erythropoietin, fetal haemoglobin concentration (HbF), and red cell 2,3-diphosphoglycerate (2,3-DPG) were measured.[10–12] An aliquot of 1 ml of venous blood was drawn every two weeks for SiEp, which was estimated using a radioimmunoassay[13]; measurements were made in duplicate and in a single batch.

STATISTICS

Data were analysed using Student's t test for difference between means, and correlation coefficients by the least mean squares best fit for linear regression. All analyses involving erythropoietin were performed after logarithmic transformation, but stated as the antilogarithmic equivalents. Qualitative differences were assessed using the χ^2 or Fisher's exact tests. Mean and standard error of the mean are given to facilitate comparison between groups.

Results

Of 24 infants studied, 14 received packed red cells (group 1) and 10 were not transfused (group 2). Indications for this intervention were failure to gain weight, lethargy, apnoea, or clinical findings suggestive of a patent ductus arteriosus when accompanied by a capillary packed cell volume reduced below 0·35. The clinical signs resolved after this procedure in all but one patient, in whom a patent ductus arteriosus murmur persisted. Six infants were transfused on two occasions.

Packed red cell transfusion resulted in an improved rate of weight gain (mean (SE) 23·3 (2·1) g/day in the week after transfusion) in six infants who were growing poorly the week before (mean (SE) 8·8 (2·8) g/day; $p<0·002$).

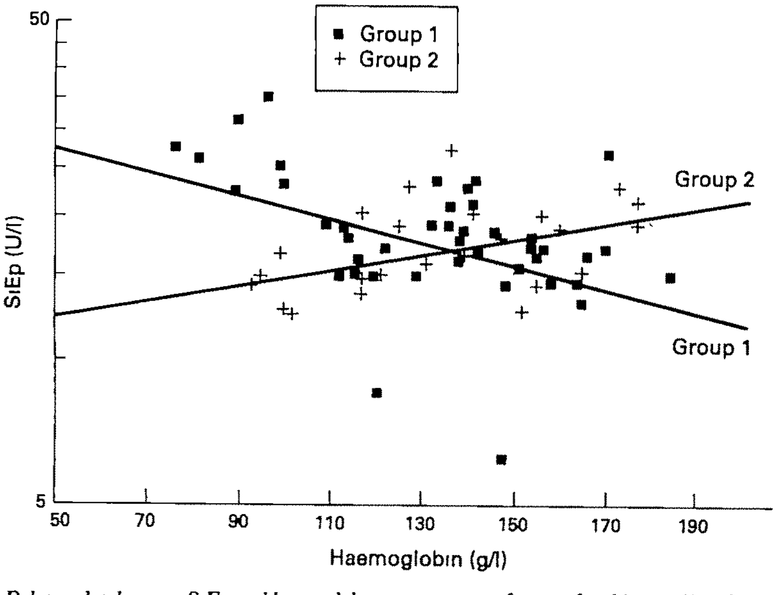
Summary of clinical and haematological data of study infants. Data are expressed as mean (SEM)

	Group 1 (n=14)		*Group 2 (n=10)*	*Significance*
Birth weight (g)	1176 (34)		1267 (33)	NS
Gestational age (weeks)	31·5 (0·3)		31·6 (0·3)	NS
Days to regain birth weight	11 (1·4)		7 (1·2)	p=0·04
Days requiring intensive care*	8·1 (1·2)		6·2 (1·3)	NS
No requiring ventilatory support	4		5	
Haemoglobin at birth (g/l)	163 (3)		183 (5)	p=0·0001
	Transfusion		*Throughout study*	
	Before	*After*		
HbF (%)	81·7 (1·9)	45·1 (5·7)	81·7 (1·9)	p=0·0001**
Red cell 2,3/DPG (nmol/ml)	4764 (289)	5460 (187)	5515 (328)	p=0·05**
FDPGF (nmol/ml)	809 (187)	2734 (296)	1070 (90)	p=0·0001**
Serum ferritin on discharge (µg/l)	336 (32)		374 (42)	
Haemoglobin at discharge (g/l)	121 (5)		101 (2·8)	p=0·003**
Days spent in hospital	51 (3)		39 (2)	p=0·004**

FDPGF=functioning diphosphoglycerate fraction

[1] Intensive care assessed as need for oxygen and/or intravenous fluids.

**Significance of difference between values before and after transfusion



Relationship between SiEp and haemoglobin concentrations for transfused (group 1) and untransfused (group 2) infants. The correlation coefficients obtained by least squares linear regression were r=−0·43, (p<0·01) and r=0·45 (p<0·05) respectively.

The mean (SE) rates of weight gain in the eight remaining infants in group 1 during the equivalent periods were 26·1 (2·6) and 24·0 (1·8) g/day respectively, which were not significantly different from those in group 2, calculated over a similar period (20·9 (3·1) and 24·9 (2·4) g/day).

The table summarises the clinical and haematological data of the infants during the study period. The two groups were comparable at delivery in terms of gestational age, birth weight, and Apgar scores. However, the mean (SD) haemoglobin concentration at birth was significantly lower in group 1 (163 (12 g/l) than in those infants who did not subsequently require a transfusion (183 (17) g/l; p=0·004). There was a significant correlation between the haemoglobin at birth and the time to the first red cell transfusion (r=0·72; $p<0·02$). The infants who required red cell transfusions took significantly longer to regain their birth weights (p=0·04). They also required intravenous fluids, ventilatory support, and supplemental oxygen for approximately two days longer than the untransfused infants, but this difference did not achieve statistical significance. Group 1, however, required a significantly longer (average 12 days) period of hospitalisation (p=0·004).

Although the mean haemoglobin concentration in group 1 was lower than that in group 2 at all times before transfusion, the rate of fall was similar in the two groups. In both groups there was a gradual upward drift in the reticulocyte count from two weeks after birth. This phenomenon seemed to disappear after transfusion, but persisted in the untransfused infants. Differences in the reticulocyte counts between the two groups did not reach statistical significance at any time.

The concentration of circulating red cell 2,3-DPG, HbF, and the calculated functioning DPG fraction (FDPGF) (the product of percentage haemoglobin A (HbA) and total red cell 2,3-DPG) were similar to those reported for a comparable group of infants.[14] Red cell transfusion resulted in the expected changes in these measurements because of the HbA content of the transfused cells (table). The measurements did not change significantly in the untransfused infants.

The range for SiEp concentration was 6·2–35·2 U/l. The geometric mean (SD) SiEp concentration for all the samples was 17·7 (1·3) U/l, which is similar to that of 17·4 (4·72) U/l for normal adults using the same assay. Significant differences between the two groups were observed when the mean SiEp concentrations were related to the haemoglobin concentrations. Thus, in the symptomatic infants (group 1) who had haemoglobin values below 120 g/l, the mean (SE) SiEp concentration was 20 (1·08) U/l, significantly higher than the concentration of 14 (1·06) U/l in the asymptomatic infants in group 2 (p=0·002). The haemoglobin concentrations in both these groups were low (104 (3·8) and 104 (3·6) g/l respectively) and not significantly different. The age at the time of sampling was also similar at 37·7 (3·5) and 36·9 (3·4) days respectively.

Appreciable differences between the two

groups were also demonstrated when log SiEp concentrations were correlated with haemoglobin concentrations (figure). In group 1 there was a significant negative correlation between the haemoglobin concentration and the log SiEp concentration ($r=-0\cdot43$; $p<0\cdot01$) for all samples analysed. This relationship did not pertain in group 2, where the correlation between the haemoglobin and SiEp was positive ($r=0\cdot45$; $p<0\cdot05$). At haemoglobin concentrations less than 120 g/l the negative correlation between log SiEp and haemoglobin concentrations in group 1 became stronger ($r=-0\cdot816$; $p<0\cdot001$), while the positive correlation in the group 2 infants became weaker ($r=0\cdot317$) and lost statistical significance. Interdependence of data points was excluded by examining the paired data for each infant at the age of 3–4 weeks, where similar correlations were obtained.

Discussion

The rapid fall in the haemoglobin concentration in preterm infants shortly after birth is referred to as the physiological anaemia of prematurity. In some instances this is not accompanied by any adverse response, when this designation may be reasonable. In contrast, a number of infants do benefit from red cell transfusions, and the anaemia in these may not be so benign. Attempts have been made to predict when benefit will accrue from such intervention, but these have so far met with limited success.

In this study we studied differences in the SiEp concentration in preterm infants who were clinically adjudged to require transfusion and those who were not, and investigated the hypothesis that these differences might provide a quantitative measure of the group at risk. Indeed, the results indicate that symptomatic infants with low haemoglobin concentrations have higher SiEp concentrations than those who are asymptomatic with corresponding degrees of anaemia. Presumably, the higher SiEp concentrations in the symptomatic infants reflect low central venous oxygen tension and tissue hypoxia[8] and would support the decision to transfuse using standard clinical criteria. This approach is strengthened by the fact that after the transfusions there was improvement in weight gain and resolution of the signs for which the red cells were infused.

Not all investigators have found red blood cells to be of benefit to the infant. Keyes *et al* reported that such a step, even when the packed cell volume was low, did not predictably alter the heart rate or respiratory rate nor decrease the frequency of bradycardia or apnoea.[15] Changes in the weight gain before and after transfusion are not stated. The SiEp concentrations in their symptomatic patients were not increased, possibly because the levels were suppressed by previous transfusions. In our patients SiEp concentrations were increased only in those patients who were symptomatic before they were transfused. It is possible that the threshold for the clinical decision to transfuse is higher in our nursery. Alternatively, as most of our infants only received one transfusion this may have been insufficient to cause suppression of the SiEp concentrations, as might have occurred with multiple transfusions in the infants studied by Keyes *et al.*

The increase in weight in certain of our infants after transfusion differs from the findings of others who failed to show this effect.[3 4] These investigators studied infants who received 'top-up' transfusions to maintain the haemoglobin concentration above 100 g/l. In contrast, the infants in our study who increased their rate of weight gain were growing poorly before this intervention. These findings suggest that selected infants may benefit from transfusion and accord with the findings of Stockman and Clark.[16] They reported that infants with haemoglobin concentrations below 75 g/l significantly increased their rate of weight gain in the week after transfusion. Although six of the 14 transfused infants showed enhanced weight gain, we were unable to demonstrate a significant difference in SiEp concentrations in these six babies compared with the eight in whom weight gain remained constant. The small number of infants in the subgroups precluded adequate analysis of the interrelationship between haemoglobin, SiEp, and weight gain. A larger study would be needed to answer this question.

A number of previous studies have examined the relationship between the haemoglobin and SiEp concentrations in preterm infants. Stockman *et al* showed a weak inverse correlation between these parameters.[8] The magnitude of the SiEp response appears to be more dependent on the position of the haemoglobin–oxygen dissociation curve and tissue oxygenation than on the absolute haemoglobin concentration. In this study we could not demonstrate a negative correlation between haemoglobin concentration and SiEp for the patients as a whole. However, once the patients were divided according to whether they were symptomatic or not, a clear inverse relationship became apparent in the former group. This suggests that only the symptomatic patients with significantly increased SiEp concentration had tissue hypoxia or higher percentages of HbF as their haemoglobin concentrations were not lower than the untransfused patients. The amounts of HbF in our patients were all similar. Previous studies have not divided patients on the basis of their symptomatology or, alternatively, have only followed up infants who were either all transfused or not transfused.

Our study suggests that some infants do benefit from red cell transfusion and that the anaemia in these babies is pathological. The reticulocyte count and haemoglobin concentrations are unhelpful in deciding which infants to transfuse. An increase SiEp concentration early in the course of the anaemia appears to be ineffectual in eliciting a reticulocyte response, but it may predict which infants would be likely candidates for treatment with recombinant erythropoietin as an alternative to transfusion. The overlap of individual SiEp values between the two groups of patients suggests that serial concentrations would be more informative than an isolated estimate. The SiEp concentrations remained constant in the asymptomatic infants throughout the study period.

Rising values in the first four weeks of life may indicate tissue hypoxia and the need for intervention by red cell infusion or, alternatively, the administration of recombinant erythropoietin. In contrast, patients with increased SiEp concentrations later on, as reported by Brown *et al*,[5] do exhibit a reticulocyte response. Intervention by transfusion in these infants would therefore seem unnecessary.

Sensitive, reliable erythropoietin assays are not readily available to the majority of centres caring for newborn infants. This study has shown that in the absence of an erythropoietin measurement it is not the haemoglobin concentration but clinical criteria, which accord with increased SiEp concentrations, that should be used to justify additional red cells for the preterm infant. The use of clinical criteria for transfusion also has limitations as it is dependent on the observer and practice varies between units.

This study was supported by the University of Cape Town Leukaemia Centre and Staff Research (Cancer and Foote) Fund, the Gwendoline Moore Trust, the Medical Research Council, the National Cancer Association, and the Michael Chanani, Kaliski and M A Richardson Bequests

We thank Keith Hart for the art work, Dr Gisela Clemons for erythropoietin assay, and Jackie Davies for help with preparation of the manuscript and its typing.

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Archives of Disease in Childhood 1992; 67: 822–825

UK experience in neonatal extracorporeal membrane oxygenation

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Abstract

Extracorporeal membrane oxygenation (ECMO) is a life support technique capable of supporting pulmonary, cardiac, or cardiopulmonary function. It has proved most successful in neonatal respiratory failure. We report the initial UK experience with a survival rate of 80% in 15 neonates (gestations 36–41 weeks, birth weights 2690–3990 g) whose condition exceeded American criteria for ECMO treatment for a prolonged period before referral. Ages at referral varied from 11 to 240 hours and the duration of bypass required varied from 30 to 240 hours respectively.

Extracorporeal membrane oxygenation (ECMO) is a life support technique that has evolved from refinements in heart-lung bypass technology. It is capable of supporting pulmonary, cardiac, or cardiopulmonary failure, sustaining life for days or weeks. It has proved to be most successful in neonatal respiratory failure. The initial experience in the USA by Bartlett *et al* was in 1975.[1] Published results on 45 newborn cases with a survival rate of 55% followed in 1982.[2] Further improved results from this and other centres rapidly followed.[3] Since 1985 the treatment has been considered standard for mature infants with severe respiratory failure in the USA and survival rates exceed 90% in some centres.[1] There are 80 centres worldwide and nearly 6000 neonates have received pulmonary support.[5] We report the initial UK experience of neonatal ECMO.

Patient selection and methods

At the Heartlink ECMO Centre (Leicester) the ECMO service started in 1989. So far a total of 28 patients have been treated; of these, 15 were neonates. Patient selection followed American guidelines.[6] Under these guidelines patients less than 34 weeks' gestation or less than 2000 g, infants with intraventricular haemorrhage, and infants that had received ventilation for more than 10 days are contraindicated. Infants with chromosomal abnormalities were considered ineligible for treatment. Patients who did not have any exclusion criteria and who had failed to respond to maximal conventional medical treatment were considered for ECMO. In America the most common indicators of failing conventional medical treatment are numerical indices such as alveolar arterial oxygen difference or, more commonly, oxygenation index is calculated according to the formula

$$\frac{\text{Mean airway pressure}\times\text{F}\text{IO}_2\ (\%)}{\text{Postductal P}\text{O}_2\ (\text{mm Hg})}$$

and if it exceeds 40 in three measurements taken at intervals of 30 minutes, ECMO is indicated. (FIO_2 is fractional inspiratory oxygen and PO_2 is oxygen tension.)

All patients received cardiac and cranial ultrasound before establishing the bypass in an attempt to exclude cyanotic heart disease and intraventricular haemorrhage respectively.

The patients referred came from centres throughout the UK and one patient was referred from Germany. Any appropriate referral was accepted if space was available. The selection criteria produced a population whose gestations were in the range 36–41 weeks and birth weights 2690–3990 (mean 3390 g).

The ECMO team is multidisciplinary and includes neonatologists, paediatric cardiologists, cardiothoracic surgeons, perfusionists, and 'extended role' nurses. Circuit design is shown in the figure. Cannulation was by surgical cutdown. The cannulae used were chosen according to the size of the patient and the type of extracorporeal life support required. Single lumen 8–14 French gauge Biomedicus or Elicath and 14 French gauge double lumen Kendall cannulae were used. Venovenous (V–V) and venoarterial (V–A) extracorporeal life support were both used. The circuits were constructed from $\frac{1}{4}$" (0·63 cm) Supertygon tubing and venous drainage was to Scimed silicon venous bladders. The bladder that was used is distensible and sits within a tripswitch, so that if venous drainage is inadequate, the collapse of the bladder inhibits pump flow. Blood was drawn from the bladders by Stockert roller pumps with Supertygon raceways. The oxygenators were Scimed 0600 or 0800 silicon membrane oxygenators capable of oxygenating up to blood flows far greater than those necessary for full cardiopulmonary support in a neonate. In the oxygenator the blood phase is separated from the gas phase by a spiralled Silastic membrane (Dow Corning). The flow of gas (or 'sweep') moves in countercurrent direction to blood flow to maximise diffusion gradients between the two phases.

Full pulmonary support requires blood flow rates in 100 ml/kg/min in V–A perfusion and

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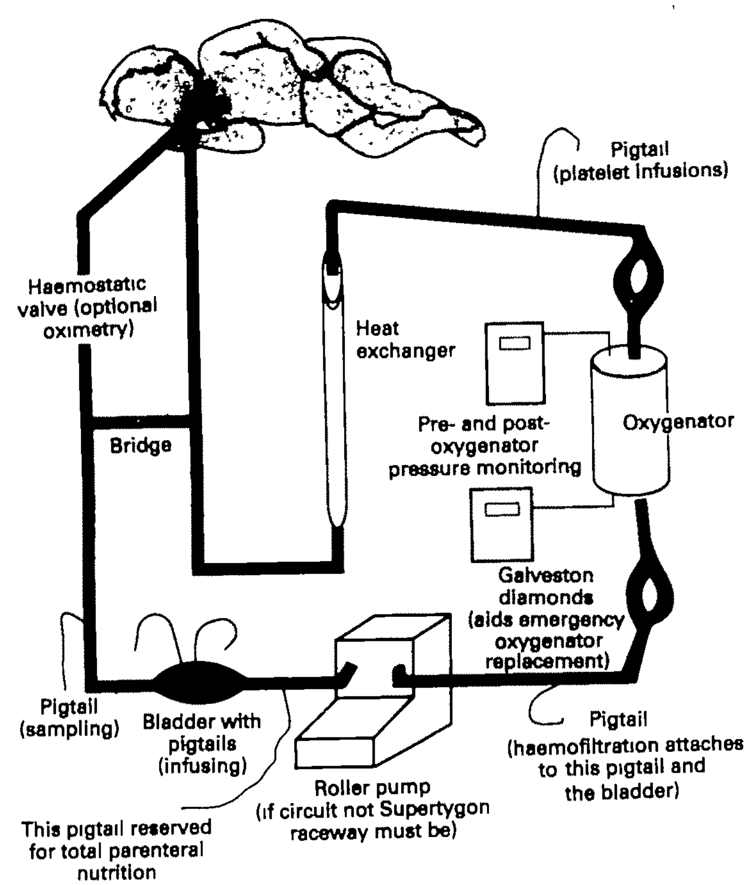
Accepted 7 January 1992



Standard neonatal ECMO circuit constructed from ¼" Supertygon.

120 ml/kg/min in V–V perfusion. Sweep gas composition was kept constant as 100% oxygen, and patient oxygenation was adjusted as a function of blood flow across the oxygenator. Under these circumstances the diffusion gradient for carbon dioxide is high and carbon dioxide clearance is mainly a function of the rate of gas flow across the membrane—the 'sweep rate'.

The heat exchangers employed were 'Cincinatti subzero' with disposable Scimed 'Ecmotherm' water columns. Patients were kept lightly sedated by an opiate infusion or by the addition of isoflurane to the sweep gas (R K Firmin *et al*, presented at European Extracorporeal Life Support Association, Paris 1991). Platelet consumption by the circuit was balanced by transfusion to keep the platelet count above 120×109/l with an optimum of 180×109/l. Anticoagulation was achieved with ah heparin bolus of 40 units/kg followed by an infusion of 20–60 units/kg/hour monitored by activated whole blood clotting time and thrombin time. The degree of anticoagulation used was enough to prolong the whole blood clotting time to 180–200 seconds (much less than that used in conventional heart–lung bypass). Daily cranial and cardiac ultrasound examinations formed part of the clinical monitoring.

Results

All the reported cases where referred for pulmonary support, conventional medical treatment having been judged by the referring centres to be failing. In most cases ECMO was considered a last resort. Twelve of the 15 patients survived (80%). The results and individual diagnoses of these patients are shown in table 1.

Table 2 summaries the illness severity of the patients referred. In our referral group, the ventilator settings by the time of referral averaged rate 65 (range 40–100) peak inspiratory pressure 43 (range 30–55) cm H_2O, positive end expiratory pressure 5 (range 4–8) cm H_2O. All were receiving 100% oxygen. The patients were receiving up to four inotropes in a variety of doses and between one and three different pulmonary vasodilators. By the time of presentation, despite this support, two patients were in a state of cardiac arrest secondary to hypoxia at the point of cannulation, both of whom survived. One patient died after referral but before ECMO.

No mechanical complications were experienced. Haemolysis was not observed in any patient. One patient had uncontrolled haemorrhage from a chest drain inserted into the lung before ECMO; a 10 day perfusion was still possible and the patient survived. One patient had subglottic oedema secondary to intubation which delayed extubation after ECMO. One patient referred at 6 days of age was left with mild bronchopulmonary dysplasia. Four patients required a total of five operations while on ECMO. These included surgical repair of total anomalous pulmonary venous connection (TAPVC), ligation of patent ductus arteriosus, and thoracotomy for haemothorax. Seizures observed in two patients before ECMO, recurred during ECMO in one case and presumably reflected an earlier hypoxic injury. One patient had a first seizure during ECMO of similar aetiology. Pre-ECMO cranial ultrasound examinations were abnormal in three patients all of whom had demonstrable periventricular flare. In all cases these appearances resolved after two days of perfusion. One patient with a normal pre-ECMO cranial ultrasound died after a catastrophic intraventricular haemorrhage.

Of the three patients that died, one had an intraventricular haemorrhage; one an irreversible pulmonary disease; and one an ischaemic gut injury, before establishing ECMO, that evolved during bypass. Much of

Table 1 UK neonatal ECMO

Case No	*Diagnosis*	*Age at referral (hours)*	*Mode of cannulation*	*Duration of bypass (hours)*	*Outcome*
1	PFC	240	V–A	130	Died
2	PFC	16	V–V	120	Died
3	MAS	24	V–V	57	Survived
4	RDS	60	V–V	115	Died
5	RDS	44	V–V	43	Survived
6	MAS	11	V–V	100	Survived
7	MAS	44	V–A	71	Survived
8	MAS	12	V–A	545	Survived
9	TAPVC	119	V–A	91	Survived
10	PFC	86	V–A	222	Survived
11	CDH	102	V–A	202	Survived
12	PFC	18	V–V	36	Survived
13	RDS	180	V–A	240	Survived
14	PFC	21	V–A	59	Survived
15	PFC	54	V–A	125	Survived

PFC=persistent fetal circulation, MAS=meconium aspiration syndrome, RDS=respiratory distress syndrome, TAPVC=total anomalous pulmonary venous connection, CDH=congenital diaphragmatic hernia.

Table 2 UK neonatal ECMO condition at cannulation

Case No	Ventilator pressure (cm H_2O)	Postductal gases (kPa)			Conventional treatment had included:				
		pH*	Pco_2*	Po_2*	High mean airway pressure	High rate (>60/min)	Paralysis	Pulmonmary vasodilators	Inotropes
1	38/3	7·35	5·78	4·4	+	+	+	+	+
2	44/4	6·7	10·8	2·5	+	+	+	+	+
3	36/4	6·7	15·6	3·9	+	+	+	+	+
4	45/4	7·2	7·9	2·3	+	+	+	+	+
5	30/5	7·29	6·2	6·5	+	+	+	+	–
6	40/5	6·9	11·6	5·4	+	+	+	+	+
7	36/3	7·49	3·06	6·3	+	–	+	+	–
8	46/4	7·48	3·7	5·3	+	+	+	+	+
9	54/3	7·65	2·8	9·8	+	+	+	+	+
10	50/4	7·51	4·2	6	+	+	+	+	+
11	42/4	7·34	5·8	2·8	+	+	+	+	+
12	45/5	7·09	8·9	10·4	+	+	+	+	+
13	60/10	7·22	9·4	6·8	+	+	+	+	+
14	36/4	7·2	6·8	2·4	+	+	–	+	–
15	35/5	7·52	3·5	3·4	+	+	+	+	+

*Fio_2 at 100%.

follow up data is at an early stage but is available on all 12 survivors. We are aware of two parents for whom there have been concern regarding development. Both received V–V support and therefore did not have carotid artery ligation. One was cannulated during cardiac arrest. The remaining 10 (age ranges 1–7 months) are reportedly developing normally.

Discussion

The numerical indices in common usage to define a treatment group for neonatal ECMO select a group whose survival with conventional treatment (from retrospective data) would be 20%. All of the patients reported had disorders far exceeding American criteria for treatment for a prolonged time before their referral (up to 100 hours). The main criterion for referral in this country has been a failure to respond to maximal conventional medical treatment. What constitutes maximal medical treatment is something that is addressed individually in each referring unit and is not restricted to indices of oxygenation. Extracorporeal circulation can efficiently remove carbon dioxide as well as oxygenate in respiratory failure.[7] The threshold for referral for ECMO seems to be falling and this has contributed to the fact that the last 11 consecutive cases have survived.

A very detailed database of all patients treated with ECMO worldwide is maintained by the participants at the Extracorporeal Life Support Organisation (ELSO) Data Registry in Ann Arbor, Michigan. Worldwide close to 6000 neonates have been treated with an overall survival of 83%. The ELSO database survival figures by diagnosis are given in table 3. Babies with diaphragmatic hernia and babies with established parenchymal lung disease have the lowest survival rates. It must be remembered that persistent fetal circulation occurs as a secondary feature of most of the diagnoses listed. The referral pattern for treatment in the UK has not followed the worldwide trends (although the sample size is small). The most striking differences are the low incidence of referrals of patients with congenital diaphragmatic hernia and sepsis (this category includes pneumonia). It is unlikely that UK pattern of disease for congenital diaphragmatic hernia differs greatly from the American experience and as UK patient numbers increase the pattern may change. It has been suggested by Professor Bartlett that ECMO is required on average for five out of every thousand neonatal intensive care admissions (R H Bartlett, presented at UK National ECMO Conference, Leicester, 1991).

Table 3 ELSO database results of neonatal ECMO

Primary diagnosis	Total No (cumulative)	Survival (%)
Meconium aspiration	2067	93
Congenital diaphragmatic hernia	996	61
Respiratory distress syndrome	788	85
Pneumonia/sepsis	752	77
Persistent fetal circulation	692	88
Air leak syndrome	22	59
Other	162	81
Total	5479	83

An 80% survival rate in this series is encouraging but not conclusive of the efficacy of ECMO. There have been two prospective trials of ECMO.[8 9] Neither used unbiased randomisation because of ethical considerations in the face of similar 80% survival rates. Results have therefore been difficult to interpret and not all authors believe the situation proved.[10–12] A randomised controlled trial is necessary for unequivocal proof of ECMO's advantages over conventional treatment[10 13] and the opportunity for this trial should be taken in the UK.

Neurological morbidity in some series has not differed from conventional medical treatment of similarly sick patients.[14] Our identified incidence of developmental delay is currently at most 13% of survivors. The degree of resultant handicap has yet to be established. Such data should be included in any future trial of ECMO. There is widespread (although not universal) feeling, which our data may support, that cannulation during cardiac arrest is associated with a high neurological morbidity and may be inadvisable.

If one accepts Bartlett's estimate of the number of patients likely to require ECMO, (R H Bartlett, presented at UK National ECMO Conference, Leicester, 1991), even at peak utilisation of ECMO in the UK most units would refer at infrequent intervals. There is therefore a limit to the number of units required by the UK. The transport of patients to an ECMO centre is associated with a mortality which should be taken into account.[15] Transport while on ECMO is possible but early referral to a centre with ECMO facilities is preferable. Preparations for a formal randomised UK trial of ECMO continue. It is anticipated that randomisation will take place at the referring centre to enable transportation risks to be evaluated.

The facilities necessary at an ECMO centre require the juxtaposition of neonatal expertise with full paediatric cardiac surgical backup, including open cardiac surgery. It is inevitable that some patients with cyanotic congenital heart disease will be cannulated for ECMO before the diagnosis is made. In our series we cannulated one baby with TAPVC despite two echocardiograms. Each scan was performed by skilled echocardiographers but performed under unfavourable conditions (portable equipment for patients with very poor echo windows due to lung hyperinflation). American centres have had similar experiences with an incidence of approximately one in 90 cases.[5] Transport for surgery while on ECMO support is different, even within an ECMO facility.

To initiate ECMO treatment costs on average £1500 per patient and our best all inclusive estimate of costs is £850 a day. This differs little from conventional treatment. We believe the financial advantage of this labour intensive alternative to conventional medical treatment may be that the duration of hospitalisation is significantly shortened. It is intended that during the prospective randomised trial of ECMO versus conventional treatment comparative costing will be formally investigated.

Conclusion

The survival rate of patients treated with ECMO in the UK appears to follow that in the USA. This is despite the fact that the neonates treated were in a far more critical condition, as judged by the America criteria for treatment for up to 100 hours before referral. ECMO seems therefore to be a potent life support resource for the sickest neonates. Despite doubts in some quarters,[11 12 16] the UK neonatal population contains infants who may benefit. We feel it is essential to proceed to a randomised trial before the same ethical constraints that precluded such a trial in the USA apply here.

We gratefully acknowledge the support and sponsorship of Heartlink, the Cardiac Childrens' Charity, who made the introduction of ECMO to the UK possible, and the assistance of the Variety Club of Great Britain.

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Addendum

Since this article was first submitted for publication the series of patients treated with ECMO in our centre has increased. The proportion of neonates among these patients has also increased (to 64%). Data from 37 neonates (from a total of 58 patients) are now available. The expected fall in the threshold for referral has not occurred but a survival rate of 80% has been maintained. The incidence of developmental delay recognised in our survivors is currently 8%. The UK prospective trial of neonatal ECMO against conventional medical treatment is due to start in September 1992.

Archives of Disease in Childhood 1992; 67: 826–830

New aerosol delivery system for neonatal ventilator circuits

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Abstract

There is mounting evidence that a variety of drugs delivered as aerosols are likely to be of benefit in neonatal units. To avoid many of the problems associated with the use of jet nebulisers in ventilator circuits, a chamber was designed to be used in conjunction with a metered dose inhaler (MDI). The dimensions (4 cm×11 cm) were chosen in an attempt to maximise drug delivery. In vitro studies were subsequently performed in order to determine the optimum operating conditions. Sodium cromoglycate delivered via this system was collected on a filter placed between the tip of an endotracheal tube and a model lung. The dose delivered was determined by means of an ultraviolet spectrophotometric assay. Using a Draeger Babylog 8000 ventilator it was found that drug delivery as maximised by actuating the device just before the inspiratory cycle when the chamber was placed adjacent to the endotracheal tube and by using a long (one second) inspiratory time. Under these conditions 1·5–2% of the original dose was deposited upon the filter at tidal volumes of 11–22 ml. When considered in terms of body weight this is many times the equivalent dose delivered to adults from an MDI. Effective drug delivery to the filter was confirmed using a radiolabelled aerosol. Radiolabelled studies delivering aerosol to the lungs of intubated rabbits demonstrated that deposition aerosol was distributed uniformly between lobes when corrected for the weight of each lobe.

In conclusion, the device appears likely to deliver significant, reproducible quantities of drug to the lower respiratory tract while being simple to use.

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Accepted 14 January 1992

A simple effective system for delivery aerosols to the lower respiratory tract of ventilated neonates may well prove to be a vaulable addition to the therapeutic options available in the neonatal unit. In particular, the ability to administer steroids in the form of an aerosol directly to the lower respiratory tract might prove to be extremely useful in ventilated neonates developing chronic lung disease. β_2 Sympathomimetics and anticholinergic agents delivered as an aerosol have been shown to have clinical effects in ventilated and spontaneously breathing neonates.[1–4] Drugs such as antioxidants and vasodilators may also be of value if they could be effectively delivered as an aerosol.

Attempts to deliver aerosols into neonatal circuits generally involve introducing jet nebulisers into the inspiratory limb of the circuit. This form of treatment has not found widespread acceptance for a number of reasons. Problems include hydroscopic growth resulting in 'raining out' within the circuit, cooling of the inspired air, great variations in nebuliser output in terms of dose delivered and size of droplets generated, and the need for a high flow rate through the nebuliser into the circuit.[5–6] Additionally there is currently no cheap, satisfactory steroid formulation available for nebulisation.

The attractions of using metered dose inhalers (MDIs) include their ease of use, the ready availability of effective steroid formulations, the resistance of drug particles to hydroscopic growth due to their surfactant coating, and the optimal size distribution of drug particles once the propellants have evaporated. They have been used in ventilator circuits for a number of years.[7–9] However, actuating the MDI directly into the endotracheal tube results in very considerable drug deposition on the adaptor and walls of the tubing due to direct impaction.[9]

To maximise drug delivery from MDIs, a chamber has been designed to be inserted into the inspiratory limb of a ventilator circuit for use with metered dose inhalers. Experiments were performed to determine the operating conditions which maximised drug delivery to the end of an endotracheal tube and to determine whether the amount of drug delivered was likely to be significant in terms of drug delivery per kg body weight. A rabbit model was used in order to determine whether an aerosol from a MDI delivered via an endotracheal tube would penetrate beyond the main bronchi in small volume lungs. This model also allowed us to assess whether aerosol deposition was likely to be distributed evenly between lobes.

Method

IN VITRO MODEL

The chamber used in these experiments consisted of a cylindrical chamber 4 cm×11 cm tapering at each end to connect into the tubing of the ventilator circuit. A valve stem was placed such that the valve orifice lay centrally within the proximal end of the chamber so that gas flowed around the valve stem as it entered the chamber. The device was introduced into the inspiratory limb of a ventilator circuit as shown in fig 1. The ventilator used was a Draeger Babylog 8000, which permitted monitoring of airway pressure and tidal volume. The visual display of the ventilator cycle enabled actuation of the MDI at specific points during the ventilator cycle. The endotracheal tube was connected to a model lung consisting of a rubber bellows that inflated and deflated during the ventilator cycle. Between the tip of the endotracheal tube and the model lung was placed a 1·2 µm Acrodisc filter (Gelman).

Experiments were performed under the following operating conditions to assess the effect upon deposition of drug at the filter: timing of the actuation during the ventilator cycle, inspiratory time, distance of the chamber from the endotracheal tube manifold, endotracheal size, and tidal volume, 'Standard' settings of 30 breaths/minute, an inspiratory:expiratory ratio of 1:1, pressures of 30/2, and a flow rate of 7·5 l/minute were used initially which produced a tidal volume, when using the 1·2 µm filter, of 11 ml. These experiments were repeated using an inspiratory:expiratory ratio of 1:3 maintaining a rate of 30 breaths per minute. In order to assess the effect of increasing the distance from chamber to endotracheal tube manifold, experiments were performed using the standard settings and actuating the MDI immediately before the inspiratory cycle when a 10 cm length of tubing was introduced between the chamber and manifold. Experiments were performed with both straight and corrugated lengths of tubing. A straight 3·2 mm internal diameter tube was used in all experiments except for one, in which a 2·7 mm tube was used using standard settings in order to assess the effect of tube size. To obtain larger tidal volumes, high inspiratory pressures were required and necessitated the use of a 5 µm filter to achieve a tidal volume of 22 ml.

Ventilator settings used for each experiment were recorded, each experiment being performed four times. Results are presented as mean (SD).

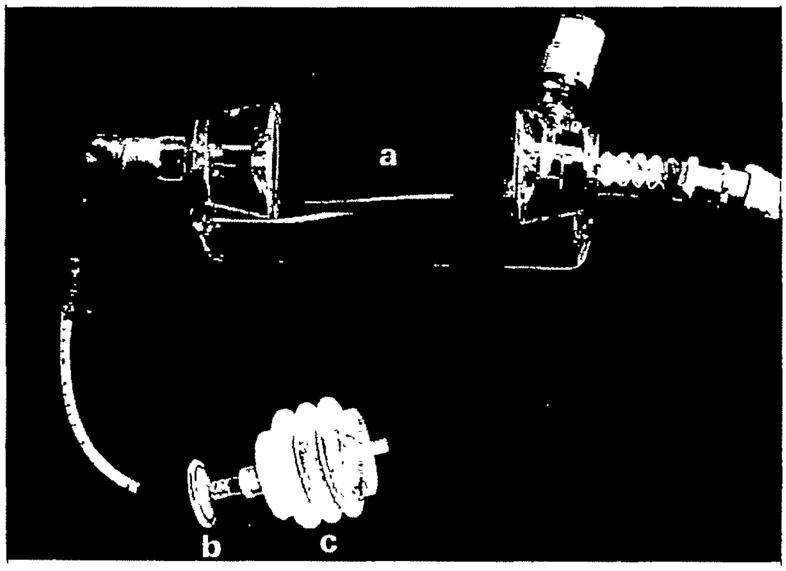

Figure 1 Chamber (a), filter (b), and model lung (c) in ventilator circuit as used in these experiments.

DRUG ASSAY

Sodium cromoglycate was used to monitor deposition of aerosol on the filter because this drug could be assayed conveniently using a ultraviolet spectrophotometric method (Hewlett Packard Diode Array spectrophotometer). For each experiment 20 actuations of a MDI delivering 1 mg sodium cromoglycate per actuation was used to ensure that sufficient drug was deposited on the filter to produce an accurate assay. Each actuation was separated by 30 seconds to ensure that the aerosol had cleared from the chamber.

At the end of each experiment the filter was initially washed with Freon 11 to remove surfactants from the surface of deposited drug particles. After drying, the filter was washed with 50 ml of distilled water. The absorbance at 326 nm was obtained for the resultant solution and this was then used to calculate the total quantity of drug 'inhaled' per actuation using the formula:

$$\text{Drug dose (mg)} = \frac{\text{Absorbance at 326 nm} \times \text{volume (ml)} \times 10}{\text{E} \times \text{number of actuations}}$$

The system had previously been calibrated using known concentrations of sodium cromoglycate, the constant E (absorbance for a 1% solution using a 1 cm path length) as 159·43. Previous experience with this method has demonstrated excellent reproducibility, this being estimated to be within 0·01 mg.

RADIOLABELLING OF NEDOCROMIL SODIUM

Technetium-99m (^{99}Tm) was used to radiolabel nedocromil sodium (Tilade, Fisons) contained in MDIs. Sodium pertechnetate in saline was eluted from a ^{99}Tm generator and then extracted into butanone. The solution was added to an empty MDI canister and then evaporated to dryness. The canister was cooled in liquid nitrogen, together with the MDI containing the drug to be labelled. The canisters were taken from the liquid nitrogen, the metering valve was removed from the drug-containing canister and the contents poured into that containing the ^{99}Tm. A metering valve was crimped onto the canister and the labelling completed with immersion in an ultrasonic bath for 10 minutes.

Nedocromil was chosen as previous work within the department using an Andersen Sampler and multistage liquid impingers confirmed that the quantity of drug and radiolabel deposited upon each stage correlated closely.

DEPOSITION OF AEROSOL WITHIN THE CIRCUIT

To assess the pattern of deposition within the chamber a single experiment was performed with the chamber operated under standard ventilator settings and actuating the MDI immediately before the inspiratory phase. After the actuation, the equipment was

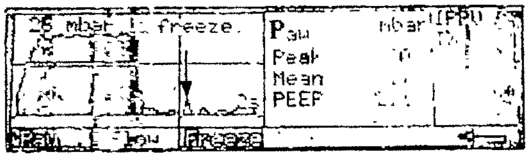

Figure 2 Visual display of Draeger Babylog 8000 ventilator showing pressure changes during one cycle of the ventilator. Pressure change due to actuation of MDI arrowed.

dismantled and the components imaged using a gamma camera. The image was displayed on a television monitor and the regions of interest defined by encompassing the image of each component. Count rates were determined, corrected for background counts, and expressed as a percentage of the total counts recorded.

RABBIT PREPARATION

Four New Zealand/Californian rabbits were studied (weight 1·99–2·17 kg). A 24 gauge catheter was inserted into the marginal ear vein and anaesthesia induced with 5 ml/kg of 20% (w/v) ethyl carbamate (urethane, Sigma Chemical Co). A tracheostomy was performed and a size 3·0 endotracheal tube inserted.

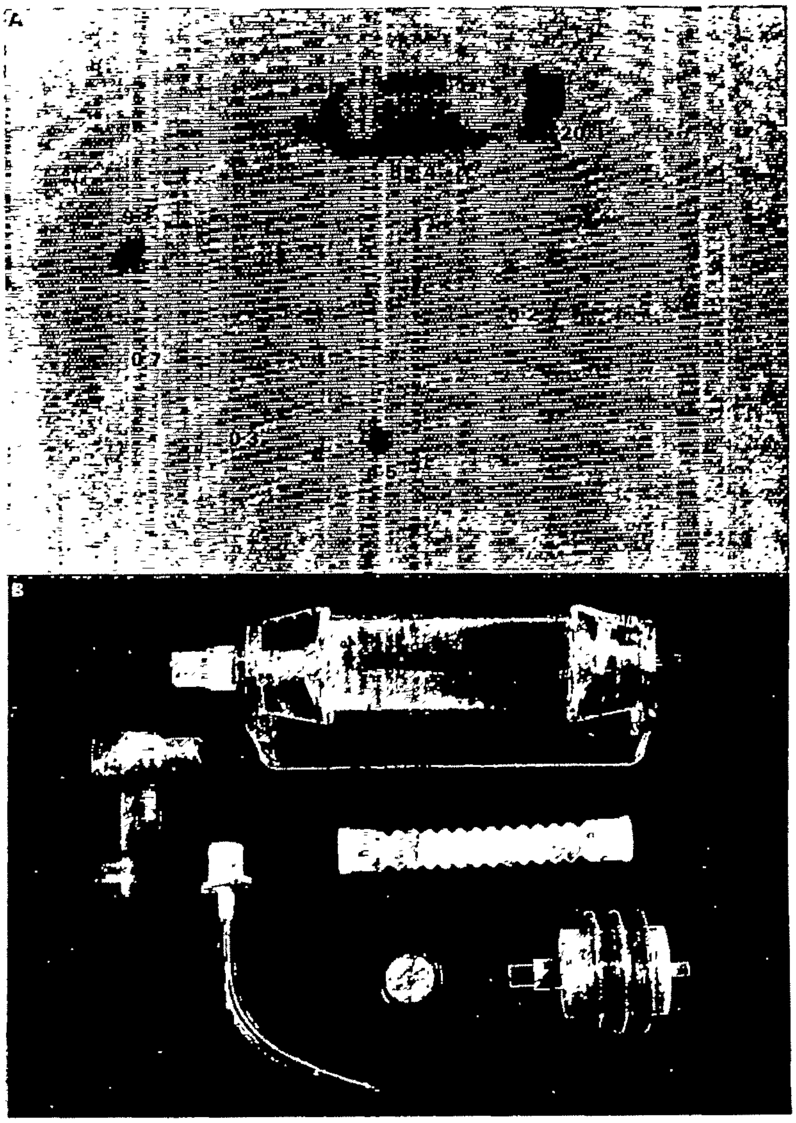

Figure 3(A) Gamma camera image of apparatus after one actuation of a radiolabelled MDI with dose deposited as a percentage of the total administered dose. (B) Apparatus as placed on gamma camera.

ADMINISTRATION OF RABIOLABELLED AEROSOL

Radiolabelled aerosol was administered via the spacing device to spontaneously breathing anaesthetised rabbits in order to determine the distribution of aerosol deposition within this animal model. It was not possible to use a ventilator circuit in these experiments and hence the chamber was connected directly onto the end of the endotracheal tube and the aerosol administered by inflating the lungs using the same technique as used in neonatal resuscitation. An air supply (4 l/minute) was connected to the distal end of the chamber by means of a T piece. After actuation of the MDI, the lungs were inflated by placing a finger over the open end of the T piece for approximately one second. This was repeated at one second intervals for a total of seven inflations per actuation. The pressure applied was sufficient to cause adequate chest wall expansion without causing apparent over expansion. This was repeated for a total of eight actuations per rabbit.

MEASUREMENTS OF AEROSOL DEPOSITION

Rabbits were killed immediately after aerosol administration. The lungs and trachea were dissected out and the lungs separated into individual lobes which were weighed. The amount of radioactivity in each lobe and the trachea and main bronchi were assayed for radioactivity. During each experiment the MDI containing the radiolabelled drug was actuated once into a plastic container. The count rate from the container and from the actuator were then used to calibrate the equipment for each experiment.

Results

Examination of the visual display on the Draeger Babylog 8000 ventilator (fig 2) showed that actuation of the metered dose inhaler increased the pressure within the airways by no more than 3 millibars. It is, therefore, unlikely to cause any problems in terms of the pressure generated within the circuit, particularly if it is actuated during the expiratory phase.

The effects of actuating the MDI immediately before or after the inspiratory phase are as follows. Using standard settings 1·54% (0·05) of the initial dose was deposited upon the filter when the MDI was actuated immediately before the inspiratory cycle but fell to 0·83% (0·10) when the MDI was fired immediately after the inspiratory cycle. When the inspiratory:expiratory ratio was altered to 1:3 at the same rate of 30 breaths/minute the dose delivered when actuating the MDI before and after the inspiratory cycle fell to 1·21% (0·02) and 0·24% (0·03) respectively. Introducing a 10 cm length of tubing between chamber and endotracheal tube manifold reduced drug deposition on the filter from 1·54% to 1·15% (0·13) for smooth tubing and to 0·89% (0·07) for the corrugated tubing.

Using a 2·5 mm internal diameter tube rather than a 3 mm tube resulted in deposition upon the filter of 1·80% (0·1). Deposition on the filter increased from 1·54% at a tidal volume of 11 ml to 1·87% (0·06) when the tidal volume was increased to 16 ml and to 2·01% (0·09) with a 22 ml tidal volume.

The gamma camera image of the radiolabelled aerosol deposition and the counts obtained from each component expressed as a percentage of the total counts in the in vitro model is shown in fig 3A. The apparatus as placed on the gamma camera is shown in fig 3B.

The dose reaching the lower airway and that penetrating beyond the main bronchi for each rabbit is shown in the table. The dose delivered per gram of lung tissue for each rabbit is also given. The mean dose deposited in each lobe as a percentage of the total dose penetrating beyond the main bronchi is shown in fig 4.

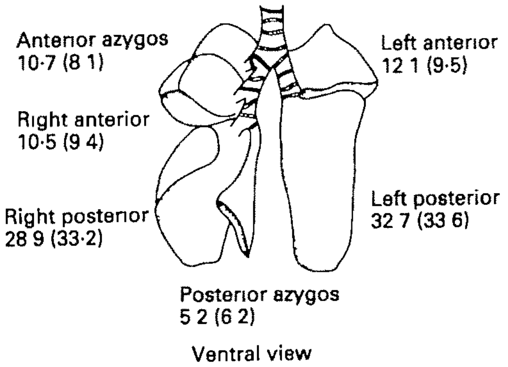

Figure 4 Mean dose delivered to each lobe expressed as a percentage of the total dose penetrating beyond the main bronchi. Mean weight of each lobe as a percentage of the total weight of the lobes is given in parentheses.

Dose of aerosol delivered to the lower respiratory tract of four rabbits as a percentage of the total administered dose

	1	*2*	*3*	*4*	*Mean (SD)*
Dose deposited in the trachea, main brochi, and lungs	12·1	13·6	8·54	6·86	10·89 (1·56)
Dose deposited in lungs	2·35	5·15	2·71	2·65	3·22 (1·30)
Dose deposited/g of lung tissue	0·29	0·40	0·24	0·26	0·29 (0·07)

Discussion

The development of a simple, effective system for delivering aerosol to the lungs of ventilated neonates offers a number of potential advances in the care of ventilated preterm infants. The most useful group of drugs used in this way may prove to be steroids. These are currently used in the treatment of ventilated neonates developing bronchopulmonary dysplasia and have been shown to have short term benefits in enabling babies to be extubated. However, most studies have failed to show a long term effect on the natural history of the disease. This may relate to both the relatively late introduction of steroids, often after three or four weeks, when significant, permanent damage has already been established and to the relatively short courses used. Both of these factors have been influenced by natural concerns regarding possible adverse effects of these drugs. A single study suggested that courses longer than 42 days may beneficially influence the natural history,[10] and recently the trend has been to resort to systemic steroids earlier in the hope that this may reduce the incidence of severe chronic disease. Indeed a recent report advocated the use of systemic steroids from day one of ventilation.[11] The early use of steroids delivered as an aerosol may result in a reduction in the incidence of chronic lung disease while offering the advantages of delivering the drug directly to its site of action, hence minimising the potential for systemic side effects.

The chamber described in this paper was designed to maximise drug delivery at the very low tidal volume observed in the neonatal patients. Since neonatal ventilator circuits are normally of the continuous flow type, the aerosol introduced into a chamber within the circuit is likely to be diluted very rapidly during the expiratory phase of the cycle and hence it is likely that only the first breath will carry a significant bolus of aerosol. The dimensions of this chamber (4 cm×11 cm) were chosen in order to maximise the aerosol concentration within the chamber[12] and hence maximise drug delivery during the first inspiratory cycle. An additional benefit of using a small chamber is that it will be much easier to handle. A similar chamber devised independently has been used to deliver radiolabelled aerosol to ventilated adults.[13] In this study, using a volume preset time cycled ventilator, it was found that approximately 5·5% of the dose from a MDI delivered via the extension chamber was deposited into the lungs, compared with only 1·2% from a jet nebuliser. Using a dosimetry technique timed with inspiration, delivery from jet nebulisers to the lungs of ventilated adults can be significantly increased.[14] However, such systems are likely to be relatively expensive and the other disadvantages of using jet nebulisers still apply. Drug delivery from a chamber such as the one described in this paper can be simply increased by further actuations of the metered dose inhaler.

Placing a chamber such as this in the inspiratory limb of the circuit rather than placing it between the endotracheal tube and the manifold as proposed by some workers will reduce drug delivery but will minimise the disturbance experienced by the neonate. Hence it may be possible to use such a device safely with acutely ill infants early in the course of the respiratory distress syndrome. The results presented here suggest that significant drug delivery can be obtained when used in this way, while the absolute dose delivered can be easily increased simply by increasing the number of actuations. These results suggest that drug delivery can be maximised by actuating the MDI immediately before the inspiratory cycle and using a longer inspiratory period. Others have described increased deposition in animal experiments when using longer inspiratory times and postulated that the longer residence period may increase deposition in the lower respiratory tract by sedimentation.[15] However, sedimentation is not likely to be a significant factor in the present experiments and hence some other effect, possibly related to the pattern of flow, may be operating. The surprisingly large drop in drug deposition at the filter when using 10 cm of smooth tubing may relate more to the timing of the actuation of the MDI. Actuating it immediately before the inspiratory phase may mean that the leading edge of the aerosol bolus has not reached the endotracheal tube manifold. More sophisticated timing of the actuation directly from the ventilator is necessary before the relationship between chamber position and actuation is further explored. The fall in drug delivery when using a smaller tube is a little surprising in view of the minimal deposition within the endotracheal tube noted on the gamma camera image. However, similar trends have been described in experiments delivering aerosols from MDIs when using different sizes of adult endotracheal tubes.[9]

The doses delivered to the filter may appear to be very small, but are in fact extremely large doses when considered in terms of body weight. Adults using a good inhaler technique may achieve drug delivery to the lower respiratory tract of perhaps 10% of the original dose delivered by the MDI, a 11 ml tidal volume might represent that of a 1 kg baby who would require only 0·14% of the original dose to receive the same dose on a per kilogram basis as a 70 kg adult. In all these experiments, even those under suboptimal conditions, the drug delivered to the filter was in excess of this dose.

The rabbits experiments show significant variations in delivery of aerosol to the lower respiratory tract when using a method of inflating the lungs similar to that used in neonatal resuscitation. Drug delivery is inevitably higher than in the in vitro studies as seven inflations were used. When used in this way the spacing chamber also acts as a holding chamber. The variation in deposition within the trachea and bronchi is considerable and may relate to factors such as the rabbit's respiratory phase during actuation and to whether the short tracheostomy tube was straight or curved at the time of actuation. The variation in dose penetrating beyond the trachea and bronchi was less pronounced while dose delivered per gram of lung tissue was remarkably consistent. The average combined weight of both lungs in an adult male is approximately 850 g[16] so that the dose delivered to the lungs of these rabbits represents more than 40 times the dose per gram of lung that may be delivered when an adult patient uses the MDI.

Distribution of aerosol to each lobe was remarkably even when correlated for the weight of each lobe despite the supine posture of the rabbits. This suggests that this form of treatment is relatively free of the gravitational effects observed when liquids are introduced into the airways via endotracheal tubes. These results, however, were obtained in animals with healthy lungs; distribution within the lower respiratory tract in clinical practice will be greatly influenced by parameters beyond the clinician's control such as ventilation defects and excessive secretions.

In conclusion, effective drug delivery to the lower respiratory tract of ventilated neonates is possible when using aerosols from MDIs delivered by a cheap, simple to use, small volume chamber introduced into the inspiratory limb of a neonatal ventilator circuit. Drug delivery may be maximised by using longer inspiratory times and by actuating the MDI immediately before the inspiratory phase when the chamber is placed close to the endotracheal tube manifold. The optimal timing if used at distances from the manifold needs to be determined. The distribution of aerosol deposition appears to be relatively uniform in healthy lungs, the dose reaching each lobe in the rabbit model correlating closely with its weight.

Dr Everard was supported by Asthma Nationwide.

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Archives of Disease in Childhood 1992; 67: 831–834

Episodic bradycardia in preterm infants

C J Upton, A D Milner, G M Stokes

Abstract

To analyse factors likely to precipitate bradycardia, 27 preterm infants born at 32 weeks' gestation or less were studied on 89 occasions. Polygraphic recordings of electrocardiography, oxygen saturation, and respiratory effort were made. Subsequently, upper airway flow was measured by a mask and pressure transducer.

In 605 episodes detected during initial recordings, time of onset of bradycardia correlated positively with apnoea duration, with bradycardia often occurring as respiratory effort resumed. Airway closure occurred in 88% of apnoeas associated with bradycardia during flow measurements, and was significantly more common than in apnoea without bradycardia (64%). We suggest that bradycardia is most commonly a reflex response to the resumption of respiratory effort against a closed upper airway as apnoea is terminated, and that this reflex is potentiated by hypoxaemia.

Bradycardia in preterm infants is extremely common and is often considered as simply a minor inconvenience. This view was encouraged by work in the 1970s which suggested that blood pressure[1] and central blood flow[2] were well maintained during bradycardic episodes in all but the most immature and sick babies. Clearly though, less mature babies are now surviving and more recent work has cast doubt on the benign nature of bradycardias. Using transcutaneous Doppler techniques, Perlman and Volpe demonstrated a fall in anterior cerebral artery flow velocity with bradycardia, which was most dramatic when the heart rate fell below 80 beats/minute.[3] Livera *et al* measured an appreciable fall in total intracerebral haemoglobin concentration during bradycardia using near infrared spectroscopy and an occasional rebound above resting values after recovery.[4] They postulated that such swings in cerebral perfusion may predispose towards the development of periventricular leucomalacia. This may explain why apnoea and bradycardia was found to be an independent risk factor for later morbidity in very low birthweight infants.[5]

When one considers such data it is surprising that so little is known about the aetiology of bradycardia. A direct effect of hypoxia on the heart was originally considered the most likely explanation.[1] Bradycardia often starts during the early stages of apnoea, however, and most authors now consider that a reflex response is more likely.[2 6 7] Our group originally postulated that reflex bradycardia was most commonly related to respiratory effort against a closed glottis during upper airway obstruction.[7] This view has been challenged by Henderson-Smart *et al*, who suggested a peripheral chemoreceptor response to falling oxygen saturation (Sao_2) was the most likely explanation.[8] Experiments on immature animals, however, have shown that heart rate changes occur at the beginning of respiratory pauses before any change in arterial blood gases.[9]

Oxygenation would appear to exert an important influence, though. We have recently reported that initial Sao_2 before the onset of apnoea is significantly lower in those episodes which result in bradycardia.[10] This study was therefore designed to analyse the relative importance of apnoea, Sao_2, and upper airway patency on the onset of bradycardia in a group of preterm infants.

Methods

Initial polygraphic recordings were made of Sao_2, electrocardiography (ECG), and two signals of respiratory effort, thoracic impedance and abdominal respiratory inductive plethysmography. A total recording time of 353 hours was analysed with a median study time of 3·96 hours (range 2·19–5·29). The recordings were viewed on a storage oscilloscope and suspicious episodes were played on to a chart recorder and analysed manually. Bradycardia was defined as an instantaneous heart rate of 90 beats/minute or less, as calculated from the R-R distance on the recordings. Full details of the methodology for these initial recordings have been described previously.[10]

Subsequently upper airway flow was measured with the infants in the right lateral position, usually within an hour of a feed. Sedation was not given. A facemask was applied over the infant's mouth and nose, with a bias flow of air of 3 l/minute conducted by tubing to one port of the mask, to eliminate dead space. The other port was connected to a pneumotachograph which could

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Accepted 17 December 1991

record the infant's respiratory flow by the use of a sensitive pressure transducer. Full details of the system for measuring upper airway flow have also been described previously.[11]

Recordings of upper airway flow, together with SaO_2, ECG, and respiratory effort, continued for about half an hour as tolerated. All data were recorded on to tape and analysed manually. In addition to bradycardias, apnoeic episodes of at least 5 seconds' duration, as detected on the flow trace, were analysed for comparison. Using a sensitive pressure transducer an artefact can be recorded during normal tidal breathing which is produced by transmission of the cardiac impulse up the patent airway. This is usually present during central apnoea in preterm infants but disappears when airway closure occurs. The presence or absence of the cardiac artefact is a reliable indicator of the patency of the upper airway, even in the absence of respiratory effort against a closed airway.[11 12] Using this system, therefore, we were able to correlate the occurrence of bradycardia with upper airway patency and oxygen saturation.

Statistical analysis was performed using simple and stepwise multiple regression analysis and the χ^2 test. Approval for the study was given by the Nottingham ethics committee and informed parental consent obtained.

Patients

Infants born at 32 weeks' gestation or less were included and were not preselected for the presence of apnoea or bradycardia. Eighty nine polygraphic recordings were made on 27 infants. Median birth weight was 1140 g (range 710–1700) and gestational age 29 weeks (range 25–32). Median day of study was 15 (range 1–55) and postconceptional age 32 weeks (range 26–36). There were 16 boys and 11 girls Eight of the infants had received mechanical ventilation for up to 10 days before entering the study but all were stable in air by the time of recording. Three infants had ultrasound evidence of intraventricular haemorrhage, although only one had parenchymal changes and all were asyptomatic. Infants were receiving treatment with theophylline for apnoea during 45 of the 89 studies. Because of the failure of some babies to settle during upper airway flow measurement, flow recordings were only possible on 83 occasions in 24 infants. The characteristics of these infants were very similar to the group as a whole.[11]

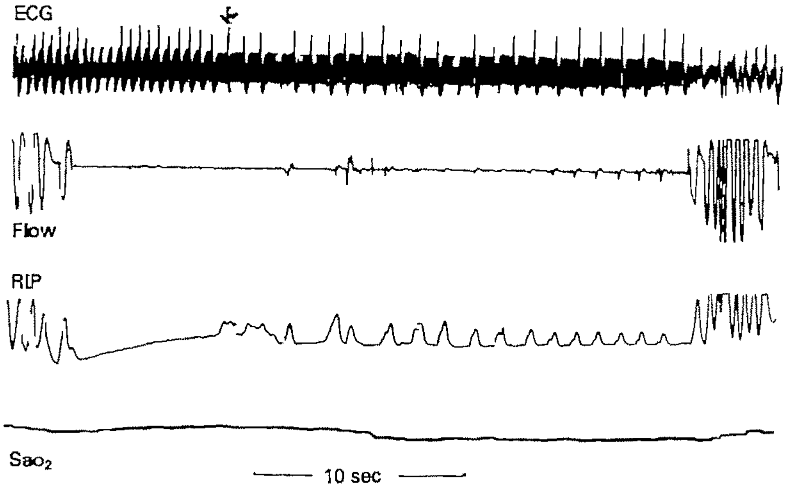

Figure 1 A prolonged mixed apnoea, with both resumption of respiratory effort and bradycardia, marked by arrow, occurring after five seconds (flow=upper airways flow, RIP=abdominal respiratory inductive plethysmography).

Results

Six hundred and five bradycardic episodes were analysed from the initial polygraphic recordings. We have previously reported that 86% of these were associated with apnoea and that the relationship between apnoea duration and minimum heart rate was poor.[10] Not suprisingly the duration of bradycardia, expressed by the number of bradycardic beats, was positively correlated with apnoea duration in seconds (number of beats=3·39+0·47×apnoea duration, r=0·49, $p<0·0001$).

There was enormous variability in the time of onset of bradycardia from the beginning of the apnoeic episode, with a range from one to 55 seconds. It seemed, though, that bradycardia commonly began as respiratory effort resumed at the end of the apnoea. This impression was confirmed by simple regression analysis with a significant positive correlation between apnoea duration and time of onset of bradycardia (onset of bradycardia=4·86+0·37×apnoea duration, r=0·55, $p<0·0001$). In other words, the longer the apnoea, the later bradycardia tends to start.

Forty one bradycardias were recorded during airway flow measurements and all were associated with apnoea. Analysis confirmed that bradycardia occurred at variable times, but often as apnoea was being terminated. Fig 1 shows a mixed apnoeic episode with a total duration of nearly 30 seconds. However, respiratory effort against a closed upper airway resumes at approximately five seconds, just as bradycardia begins. Apnoea was present on the flow trace in all 41 episodes in which bradycardia occurred. Median apnoea duration was 14 seconds (range 2–51) with bradycardia occurring after a median 11 seconds of apnoea (range 1–34). The relationship between the time of onset of bradycardia and apnoea duration for these episodes is shown in fig 2. This confirms a strong positive correlation (r =0·73, $p<0·0001$).

We have previously reported the effect of SaO_2 on the onset of bradycardia during the polygraphic recordings. Median baseline SaO_2 was lower and the fall in SaO_2 with apnoea was greater during bradycardia compared with non-bradycardic episodes.[10] However, it is difficult to understand how the temporal relationship between the termination of apnoea and onset of bradycardia could be explained on the basis of falling SaO_2 and therefore later onset of bradycardia. This suggests that the fall in SaO_2 is not the primary factor which precipitates bradycardia. To analyse this further we performed stepwise multiple regres-

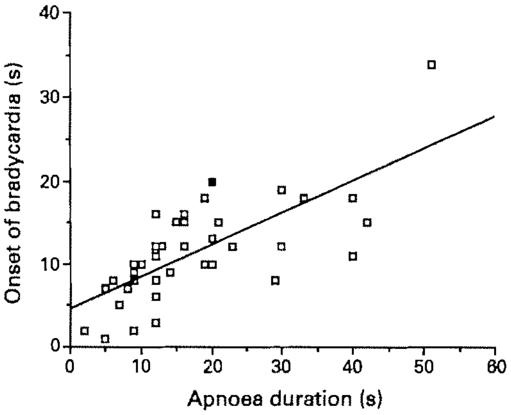

Figure 2 Time of onset of bradycardia from the beginning of apnoea(s) plotted against apnoea duration(s). Onset of bradycardia =4·54+0·39×apnoea duration, r=0·73, p<0·0001.

sion analyses on both polygraphic recordings and airway flow data. This showed no effect of either baseline Sao_2 or the fall in Sao_2 with apnoea, on the timing of bradycardia, once allowance had been made for apnoea duration.

Upper airway patency, however, is a potentially important factor. We therefore compared the 41 bradycardias with 277 episodes of apnoea lasting at least five seconds on the flow trace during which no bradycardia occurred. Upper airway closure, as detected by the absence of the cardiac artefact, occurred during 36 of 41 apnoeas associated with bradycardia (88% of the total). It occurred only in 178 of 277 episodes without bradycardia (64% of the total). Upper airway closure, therefore, occurred significantly more frequently during bradycardia (p=0·005, χ^2 test). Apnoea associated with bradycardia was consequently more likely to be mixed in character with 61% in the bradycardic and 36% in the non-bradycardic group being mixed episodes (p<0·01, χ^2 test).

Discussion

The inter-relationships between apnoea, Sao_2, airway patency, and bradycardia are clearly complex. Henderson-Smart *et al* suggested that a fall in Sao_2 was the main precipitant of reflex bradycardia.[8] Using a conventional six seconds averaging time on our oximeter, we were unable to study the temporal relationship between the fall in Sao_2 and the onset of bradycardia. However, it is difficult to explain the relationship between the onset of bradycardia and termination of apnoea on the basis of falling Sao_2: bradycardia occurs later in longer apnoea where the Sao_2 drop is greater. However, the data of Henderson-Smart *et al* do confirm that bradycardia tends to occur later with longer apnoea; at a mean of 6·2 seconds in apnoeas of 10–14 seconds and at 11·85 seconds in apnoeas of greater than 20 seconds.[8] They did not discuss why this should be. It is possible that both bradycardia and the fall in Sao_2 are reflex responses to respiratory effort against a closed upper airway. It has been demonstrated in older infants that episodes of apnoea with an obstructive element produce more rapid desaturation than central apnoea.[13] In common with others,[14] however, we have been unable to confirm this in preterm infants.[11]

In 86% of bradycardias in the polygraphic recordings apnoea was present, as detected by the absence of respiratory effort. The true figure is probably much nearer 100%, as many bradycardias in this part of the study were associated with disorganised and high amplitude respiratory effort which we have seen is common during mixed or obstructive apnoea.[11] Indeed, all bradycardias recorded with airway flow measurements were associated with apnoeic episodes, which were often very short. This was also noted previously in the study of Vyas *et al.*[7]

Vyas *et al* first suggested that airway closure was important in the pathogenesis of bradycardia. We have confirmed this, showing airway closure is significantly more common during apnoeas with bradycardia than those without. We have also demonstrated that there is a close temporal relationship between the onset of bradycardia and the resumption of respiratory effort. It would appear that the original observations of Vyas *et al* are substantially correct: that bradycardia is common when respiratory effort resumes against a closed upper airway.

Sao_2 is clearly important, though, as demonstrated by the fact that a low baseline Sao_2 is more likely to produce bradycardia during apnoea. It has also been shown that laryngeal chemoreflex bradycardia, another vagal reflex, is potentiated in conditions of relative hypoxia, at least in older infants.[15] We therefore postulate that reflex bradycardia as a result of respiratory efforts against a closed upper airway is potentiated in the presence of relative hypoxaemia.

Mixed apnoea occurs in the presence of a closed upper airway and, being generally longer than central apnoea, commonly produces desaturation. It is, therefore, particularly likely for mixed apnoea to result in bradycardia. We suggest that the patency of the upper airway is much more important than has previously been realised in the prevention of morbidity from apnoea and bradycardia in preterm infants. Continuous positive airway pressure, which seems to act by splinting open the upper airway,[16] should therefore be considered in all preterm infants with problematical apnoea and bradycardia.

Dr Upton was supported by a grant from the Medical Research Council of Great Britain

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Archives of Disease in Childhood 1992; 67: 835–839

Cerebrovascular carbon dioxide reactivity and failure of autoregulation in preterm infants

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Accepted 6 February 1992

Abstract

Changes in cerebral blood flow velocity (CBFV) in response to a rise in arterial carbon dioxide tension ($Paco_2$) in 94 ventilated preterm infants were determined using Doppler ultrasound to assess whether the nature of this change might predict subsequent neurological injury. Concomitant changes in mean arterial pressure (MAP) were recorded. Both CBFV and MAP rose significantly in response to the rise in $Paco_2$, the response being significantly less in the first 24 hours. Analysis indicated that the change in CBFV in the first day of life in infants ≤30 weeks' gestation was dependent to a great extent on the concomitant change in MAP. Similar dependence also occurred after administration of pancuronium to infants whose CBFV response was previously independent of changes in MAP. This dependency lasted for the duration of paralysis. Changes in CBFV after a rise in $Paco_2$ did not predict subsequent neurological injury. The influence of pancuronium on cerebrovascular regulation warrants further study.

Periventricular leucomalacia (PVL) is an important cause of cerebral palsy especially in sick preterm infants. It results from infarction of the periventricular white matter,[1] which is a relative vascular watershed. It has been hypothesised that PVL develops if cerebral blood flow is not regulated in the face of changes in blood pressure,[2] but the exact pathophysiology of its development remains incompletely understood. Little is known about the degree to which preterm infants are capable of regulating cerebral blood flow, or whether the extreme preterm infants who now constitute an increasing proportion of the workload of neonatal intensive care units respond differently to their more mature counterparts.

An important factor mediating cerebral blood flow is arterial carbon dioxide tension ($Paco_2$). The rise in cerebral blood flow in adults,[3] which accompanies a rise in $Paco_2$, also occurs in preterm neonates.[4] However, six of the 19 infants in the latter study had an unexpected response, with cerebral blood flow (assessed with Doppler ultrasound) falling as $Paco_2$ rose (approximately 1 kPa). Of these six infants, three subsequently developed PVL, whereas all of the remaining infants, who showed either no change or a rise in cerebral blood flow velocity (CBFV), had normal cranial ultrasound appearances.

We therefore wished to assess whether the changes in CBFV induced by a rise in $Paco_2$ might predict subsequent development of PVL in a large group of ventilated preterm infants.

Patients and methods

The study was performed on the neonatal unit at the Leicester Royal Infirmary. All infants of ≤34 weeks' gestation who were ventilated for idiopathic respiratory distress syndrome (IRDS) were considered eligible. It is our practice for all such infants to have indwelling arterial catheters (either umbilical or peripheral) for blood gas sampling and blood pressure monitoring. Infants were not studied if their condition was considered unstable, if their initial $Paco_2$ was >7kPa, if there was no indwelling arterial line, or if there were cranial ultrasound abnormalities at the time of their first study. Infants were studied as soon as possible after birth and daily thereafter until extubation. The study was approved by the Leicestershire district ethics committee and informed parental consent was obtained before enrolling infants in the study.

STUDY PROCEDURE

Before each study the following measurements were recorded:

Blood pressure

Blood pressure was measured by a pressure transducer (Spectramed P23XL) attached via non-compliant manometer tubing to the infant's indwelling arterial line as previously described.[5] A permanent record of blood pressure was made on a chart recorder (Gould) and mean arterial pressure (MAP) noted.

Cerebral blood flow velocity

In all infants, CBFV recordings were made from one anterior cerebral artery (ACA) using an ATL 600 duplex Doppler system with a 724A probe (pulse echo 7·5 MHz, Doppler frequency 5 MHz). The ACA was visualised in the sagittal plane through the anterior fontanelle and signals were recorded from a point midway between the inferior-most border of the corpus callosum and the vessel's origin from the circle of Willis. Care was taken to ensure that the angle of insonation of the vessel was less than 10°.

For these recordings the Doppler sample volume was set to 3 mm and the high pass wall filter at its lowest value (100 Hz). The ultrasound intensity was kept as low as possible and never allowed to exceed 100 mW/cm^2 SPTA. Doppler signals were recorded onto digital audiotape and subsequently replayed through a fast Fourier transform analyser.[6] The maximum frequency envelope of 20 or more consecutive beats were extracted and calibrated in terms of velocity using the Doppler equation. The mean velocity over the cardiac cycle was estimated by taking the mean value of the maximum velocity over the cycle.[7]

Ventilatory recordings

Ventilator settings and whether the infant was paralysed with pancuronium at the time of the study were recorded. Before each study, 0·2 ml of blood was taken from the infant's arterial line for Paco$_2$ and arterial oxygen tension (Pao$_2$) determinations. Routine sedation with an opiate was not used during the course of this study.

Carbon dioxide challenge

The Paco$_2$ was then raised (approximately 1 kPa) by placing a 5–15 ml deadspace (depending on the weight of the infant) into the ventilator circuit between the ventilator manifold and the end of the endotracheal tube. The deadspace was made of wide bore non-compliant tubing and was shown to be of negligible resistance compared with the endotracheal tube. To confirm that the use of such a deadspace did not affect the ventilator pressures being delivered, airway pressure was measured using a butterfly needle inserted into the endotracheal tube, attached to a pressure transducer (Spectramed P23XL). The Paco$_2$ was then allowed to equilibrate for 10-15 minutes, the change being monitored where possible by a transcutaneous carbon dioxide electrode. A further 0·2 ml of blood was taken for repeat blood gas analysis, and then repeat MAP and CBFV recordings were made as before.

Real time ultrasound

Cranial ultrasound appearances were noted daily at the time of each study. After extubation, scans were performed twice each week in the first two weeks after birth and subsequently once each week until discharge. Scans were classified as previously reported[8]; either normal, or showing haemorrhage and/or PVL, the latter being subdivided into prolonged flare or cystic degeneration.

During the study period, 104 infants of suitable gestational age were ventilated for IRDS. Of these, one was excluded because of multiple congenital abnormalities including microcephaly. Three infants died within the first two days of life without being studied, as their condition was judged to be too unstable. CBFV recordings from four infants were unable to be analysed for technical reasons and two infants referred from other hospitals had existing cranial ultrasound abnormalities at the time of referral. The remaining 94 infants were studied on a total of 382 occasions. Their gestational age ranged from 25 to 34 weeks and postnatal age from 2 to 335 hours. Eighty two infants were studied on at least two occasions and the first study was performed at a mean of 15·6 hours after birth.

ANALYSIS

The results for each day of life were analysed separately using linear regression to examine the factors influencing changes in CBFV for a standardised change in Paco$_2$ of 1 kPa. A step down analysis was used, incorporating MAP, heart rate, and Pao$_2$ as potential explanatory variables. The adequacy of the linear model was checked by plotting residuals. Mann–Whitney tests were used to compare changes in these variables in infants with and without subsequent cranial ultrasound abnormalities. The effect of gestational age on these changes was also examined. Longitudinal analysis (within subject) was performed using paired *t* tests to compare changes in CBFV, MAP, and Pao$_2$ with the lower and higher Paco$_2$ values at different postnatal ages. No adjustment was made for multiple comparisons. The principal findings would not have been altered by this adjustment, which was judged unnecessary because of the small number of comparisons being made. The effects of gestational age was assessed by dividing the infants into two groups: those ≤30 weeks and those ≥31 weeks.

Results

The following changes were observed in the first week of life.

BASELINE MEASUREMENTS (FIGS 1 AND 2)

Mean baseline CBFV and MAP rose by 46% (2 cm/s) and 11% (4 mm Hg) respectively between the first and second days of life ($p<0·001$, $p=0·01$ respectively). MAP rose by a further 10% (4 mm Hg) over the subsequent 24 hours ($p=0·001$). Baseline Paco$_2$ changed little throughout the first week, with somewhat larger day to day variations in Pao$_2$. CBFV was not affected by gestation, but MAP was significantly higher in infants ≥31 weeks compared to those ≤30 weeks ($p=0·01$) throughout the first week.

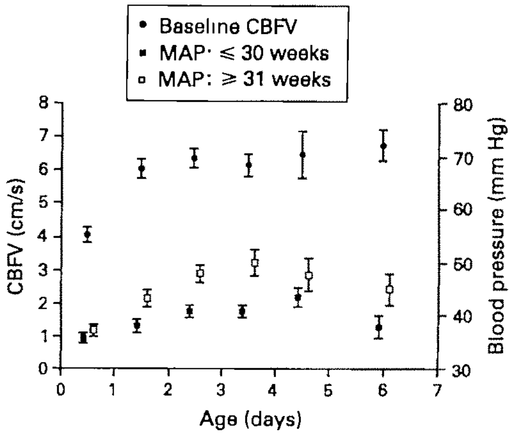

Figure 1 Baseline CBFV and MAP over the first week of life. MAP was significantly higher in infants ≥31 weeks' gestation compared with those ≤30 weeks. Points are mean (SEM).

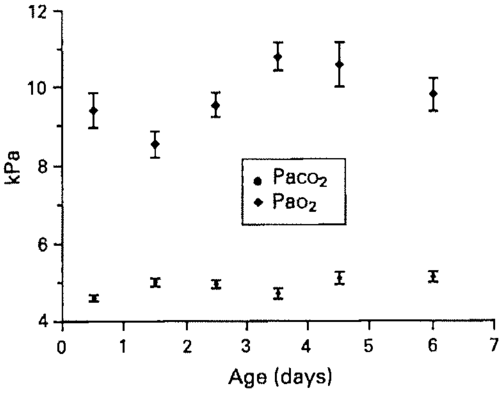

Figure 2 Baseline Paco$_2$ and Pao$_2$. Points are mean (SEM).

RESPONSE TO INCREASED Paco$_2$ (TABLE)

The mean induced change in the Paco$_2$ remained relatively constant from day to day. The mean (SEM) rise in CBFV (for a standardised rise in Paco$_2$ of 1 kPa) was 1·1 (0·3) cm/s during the first 24 hours after birth. This represented a mean increase of 33% from baseline CBFV ($p<0·001$). During the subsequent 24 hours, the mean (SEM) rise in CBFV was 2·1 (0·4) cm/s which was significantly greater (53%, $p=0·001$). Overall, CBFV rose on 322 occasions, fell on 35 occasions (28 infants) and showed no change on 25 occasions (21 infants). No infant showed a fall in CBFV on every occasion studied. The CBFV response was not influenced by gestational age.

Overall, the change in MAP was highly significant ($p<0·001$), rising on 281 occasions, falling on 74 occasions (53 infants), and showing no change on 27 occasions (24 infants). The mean (SEM) rise in MAP was less during the first 24 hours of life (1·5 (0·4) mm Hg) compared with subsequent days (2·4 (0·5) mm Hg) but was unaffected by gestation. The contrast between day 1 and day 2 is of doubtful significance in view of the multiple comparisons performed. The fall in MAP was accompanied by a fall in CBFV on 12 occasions in 11 infants, all of whom were ≤30 weeks. On the other occasions when MAP fell, CBFV either remained constant or rose. This occurred in infants of all gestations.

Accompanying significant changes in Pao$_2$ occurred (mean (SEM) rise 1·7 (0·6) kPa) in the first 24 hours ($p=0·006$), but thereafter were not significant. This response was also unaffected by gestation.

Interrelationship of factors in the carbon dioxide response

Factors affecting the CBFV response to the rise in Paco$_2$ varied with both postnatal and gestational age. For infants ≤30 weeks, during the first 24 hours after birth the change in CBFV in response to the rise in Paco$_2$ depended significantly on the accompanying changes in MAP ($p<0·001$, regression coefficient 0·69, SD 0·12) to which 53% of the variability (coefficient of determination) in CBFV was attributable (changes in Paco$_2$ and Pao$_2$ being included in the regression model). This relationship was not significant after the first 24 hours in these infants, or for infants ≥31 weeks both during and after the first 24 hours.

Mean rise in Paco$_2$ induced and resulting percentage rises in CBFV and MAP (all infants)

	Age (days)					
	1	*2*	*3*	*4*	*5*	*6–7*
ΔPaco$_2$ (kPa)	1·1	1·2	1·1	1·2	0·9	1·1
ΔCBFV/Δco$_2$ (%)	33 *	53	49	55	52	51
ΔMAPV/Δco$_2$ (%)	5·2 †	7·6	7·7	8·1	8·6	8·6

Statistical analysis on days 1 and 2. *$p=0·001$, †$p=0·04$

EFFECTS OF PANCURONIUM

There were 31 infants in the group who received pancuronium to facilitate ventilation after they had been studied on at least one occasion. Of these, 22 had at least two studies while paralysed and at least one further study performed after stopping pancuronium. The decision to use pancuronium was made independently by the clinicians responsible for the infants' care. The gestational ages of the infants on pancuronium were representative of the study group as a whole, as were their baseline values of CBFV, MAP, Paco$_2$, and the CBFV and MAP responses to the rise in Paco$_2$.

Analyses were performed as previously, comparing the infants' response to the rise in Paco$_2$ before administration to pancuronium (mean postnatal age 10 hours), while paralysed (mean ages 41 and 65 hours) and after stopping paralysis (mean age 119 hours). Before paralysis, changes in CBFV following the rise in Paco$_2$ were not significantly dependent on MAP, regardless of gestation. After administration of pancuronium changes in CBFV were dependent on MAP ($p=0·015$, regression coefficient 0·84, SD 0·31), with 28% of the variability in CBFV due to changes in MAP. This dependence persisted for the duration of paralysis ($p=0·014$), but was not significant after cessation of paralysis. This was independent of gestation.

PREDICTIVE VALUE OF THE CARBON DIOXIDE RESPONSE

Twenty seven infants (28·7%) developed mild intraventricular haemorrhage and a further four had severe haemorrhage with parenchymal involvement. Twenty one infants (22%) had prolonged flare on cranial ultrasound, of whom nine (9·6%) subsequently developed cystic changes. One further infant developed a single small periventricular cyst without preceding flare. The change in CBFV did not predict subsequent development of haemorrhage ($p>0·21$), prolonged flare ($p>0·33$) or cystic PVL ($p>0·36$), even in gestational age subgroups.

Discussion

Studies involving the effects of carbon dioxide on the circulation are beset with difficulties, with important ethical and methodological considerations, concerning the degree of Paco$_2$ manipulation and the way in which this is achieved. The method that we have used allowed us to both change the $Paco_2$ by a significant amount (while remaining within the normally accepted range) and achieve a steady state at the higher level rapidly and consistently, without having to adjust ventilator settings. The latter method would have direct effects on Pao_2, which may be detrimental to the infant in addition to potential secondary effects on cardiac function.[9 10]

A second important consideration is the method used for estimation of cerebral blood flow. Changes in CBFV have been shown to correlate well with actual changes in cerebral blood flow.[11] In addition, studies examining the relative vasodilatory effects of changes in $Paco_2$ on cerebral vessels indicate that the smallest pial vessels exhibit the highest degree of dilatation.[12 13] In contrast to these surface vessels, intracerebral (parenchymal) vessels show relatively little change[14] and it may therefore be concluded that most of the cerebral blood flow regulation in response to changes in $Paco_2$ takes place at the level of these small vessels. Therefore using changes in CBFV in proximal major cerebral vessels as an estimation of changes in actual cerebral flow in response to changes in $Paco_2$ appears valid.

The characteristics of the infants we have studied are representative of the populations seen in most neonatal intensive care units. Mean baseline values of CBFV and MAP are comparable with published normal ranges.[15 16] The 46% rise in baseline CBFV between the first and second days did not appear to be due to the concomitant 11% rise in baseline blood pressure and subsequent rises in blood pressure were not associated with significant changes in baseline CBFV.

The factors on which the changes in CBFV in response to the rise in $Paco_2$ depended altered significantly with both gestation and postnatal age. Our data indicate that in the first 24 hours after birth, extremely preterm infants (≤30 weeks' gestation) demonstrate changes in cerebral blood flow in response to a rise in $Paco_2$ which are dependent to a great extent on concomitant changes in blood pressure. They are therefore potentially at greater risk from sustaining ischaemic injury than their more mature counterparts. The mechanisms responsible for this difference remain unclear. The transition to extrauterine life most obviously entails loss of the placental circulation, which in utero tends to damp down circulatory changes due to variations in fetal cardiac output.[17] After birth, if vasomotor tone is insufficiently mature, changes in blood pressure may directly affect organ blood flow. Reasons for the loss of this pressure passivity in the less mature infants after the first 24 hours are also unclear. However, while neurogenic and humoral mechanisms are thought to play a relatively minor part in the regulation of cerebral blood flow under normal circumstances,[13 19] under conditions of stress and in the presence of immature vasomotor tone[20] they may have a more influential role. In addition, the catecholamine surge around the time of birth has been shown to influence the behaviour of receptors in lung tissue[21 22] and similar responses may well be induced in other tissues, such as the brain.

Similarly, involvement of neurogenic and humoral factors may be responsible for the changes we have observed after administration of pancuronium. Roizen *et al* demonstrated that administration of pancuronium resulted in a fall in plasma noradrenaline concentrations in adults, which they felt resulted from a generalised reduction in sympathetic outflow.[23] There is conflicting evidence in this area, since others have demonstrated both a direct and an indirect sympathomimetic response to the administration of pancuronium.[24 25] We have recently found that paralysed infants demonstrated pressure passive changes in CBFV at fast ventilator rates, when the $Paco_2$ was raised using a deadspace.[26] However, this higher $Paco_2$ level was not significantly different from that when the infants were ventilated at slow rates, yet at the slower rate CBFV was not blood pressure dependent. It may be that the loss of autoregulation to a $Paco_2$ challenge which we found in those infants was not a function of fast ventilator rates as we suspected, but rather was related to the use of pancuronium. Our findings of a potential adverse effect of pancuronium in terms of preterm cerebral injury contrasts with previous work[27] which suggested a beneficial effect in terms of prevention of intraventricular haemorrhage. Clearly caution must be exercised in attaching clinical significance to an unexpected finding on statistical analysis, but we feel the effects of pancuronium in the preterm neonate warrant further study.

While these results are also comparable with our previous study,[4] they are at variance with those of Pryds *et al*.[28] Using an intravenous xenon-133 technique to measure cerebral blood flow, they found a large increase in the change in flow for a standardised rise in $Paco_2$ between the first and second days of life (11·5 and 32·6% respectively), though again the numbers studied on two occasions were small. These values are lower than others have found using a similar method for assessing cerebral blood flow.[29] Baseline $Paco_2$ rose significantly between the first and second days and the absolute change in $Paco_2$ used (±0·5 kPa) before standardisation to 1 kPa was smaller than in our study, and was achieved by unspecified 'ventilator manipulation'. In view of the potential effects on cardiac output and hence blood pressure that such manoeuvres might engender, it is interesting to note that no specific relation of $Paco_2$ to blood pressure was noted. Finally, all the infants in that study were paralysed with pancuronium. Clearly the potential effects of pancuronium we have suggested may have influenced their results. In addition, all of the infants in their study received phenobarbitone as part of their management and although conflicting evidence exists, the use of barbiturates may well affect the cerebrovascular carbon dioxide response, mediated by an effect on brain metabolic rate.[30]

The failure of our carbon dioxide 'stress' to identity infants who subsequently developed ultrasound evidence of PVL may have been due to several factors. All infants were studied when stable, and thus the carbon dioxide response would have been unaffected by the acute clinical problems to which development of PVL has been shown to be related.[31] This is unlike the fixed alteration in the carbon dioxide response that occurs in adults with cerebrovascular disease.[32]

In conclusion, we believe there are important implications to our findings that changes in CBFV (which we believe represent changes in cerebral blood flow) after changes in $PaCO_2$ are greatly influenced by accompanying changes in blood pressure both in infants ≤30 weeks' gestation within the first 24 hours after birth and in infants on pancuronium. Since such pressure dependence of flow has been linked to subsequent neurodevelopmental injury, it is clearly important that accurate, continuous monitoring of blood pressure and avoidance of large pressure changes is carried out in these potentially at risk infants.

AC Fenton is supported by the Spastics Society

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Archives of Disease in Childhood 1992; 67: 840–845

Traumatic neonatal intracranial bleeding and stroke

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Abstract

Ischaemia within the regions supplied by vertebral and posterior cerebral arteries has been described as a complication of birth injury, either by direct trauma or by compression from a herniated temporal uncus. Ischaemia within the territory of the middle cerebral artery has been documented after a stretch injury of the vessel's elastica interna. From a series of seven personal observations on birth trauma and related cerebral stroke, we describe three neonates with the uncal herniation type of occipital stroke and four infants with hypoperfusion of the middle cerebral artery or one of its major branches. In three of the latter a basal convexity subdural haemorrhage probably induced the ischaemia, whereas in the other it was associated with haemorrhagic contusion of the parietal lobe. Experimental work and reports on older children support the idea that vasospasm due to surrounding extravasated blood can be one of the responsible mechanisms. Both forceps delivery and difficult vacuum extraction can be implicated in this supratentorial injury, leading to permanent neurological damage in at least half of the survivors in this series.

Arterial cerebral infarction has become a frequent diagnosis in the newborn. At postmortem examination its incidence can be 17% in term neonates.[1] Diverse aetiopathogenic mechanisms generate this lesion.[1–8] Several authors have drawn attention to elusive neonatal arterial cerebral occlusion.[9–11] Emphasis has been put on a characteristic presentation with seizures, either focal or general.[3 4 5 8 12]

Mechanical birth trauma has been recognised as a direct cause of intracranial arterial injury in four different patterns: laceration of the middle meningeal artery after difficult instrumental delivery[13]; stretch injury of the vertebral artery and its branches[14]; occlusion of the posterior cerebral artery after uncal herniation due to intracranial hypertension[15 16]; and finally, stretch injury of the middle cerebral artery in the absence of supratentorial subdural bleeding.[17] From a review of 10 patients described in the literature and seven personal observations showing an association of traumatic intracranial bleeding and arterial cerebral ischaemia, we propose yet another pathogenesis: supratentorial basal convexity subdural haematoma and subsequent occlusion of the middle cerebral artery. Haemorrhagic contusion of the parietal lobe due to depression of fractured bone fragments could also be contributive.

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Accepted 6 February 1992

Case reports

CASE 1

This girl, the second of female twins, was delivered at 38 weeks of gestation with three emergency vacuum tractions because of fetal bradycardia. Her Apgar scores were 4 and 6 at 1 and 5 minutes. She weighed 2270 g at birth and was referred promptly because of subgaleal haemorrhage with hypovolaemic shock. Neither seizures nor intracranial hypertension were part of her clinical evolution. A computed tomogram confirmed the epicranial bleeding and revealed small ventricle cavities, dehiscence between the left parietal and occipital bone, as well as a distinct extracerebral haemorrhage overlying the left tentorial leaflet adjacent to the posterior falx and left occipital cerebral lobe (fig 1A). A repeat computed tomogram on day 8, taken because of focal electroencephalographic (EEG) disturbances demonstrated residual subdural blood and additional marked hypodensity of the left parietotemporal area (fig 1B). A Doppler ultrasound scan showed symmetrical flow velocities in both middle cerebral arteries. At the age of 6 months the ultrasound image of the brain was symmetrically normal but detailed neurological examination suggested a mild right spastic hemiplegia.

CASE 2

After an uneventful pregnancy this firstborn boy was delivered at term with a difficult vaginal delivery complicated by persistent occipitoposterior position, a long second stage (135 minutes) and failed forceps traction. Nevertheless his Apgar score was 9 at 1 and 5 minutes. He weighed 3450 g. Obvious neonatal problems were not recorded. Pathological density of the right temporal region on the ultrasound scan prompted computed tomography on the sixth day. The right tentorial leaflet appeared covered with blood, extending into the cerebral parenchyma of the temporal and occipital lobes. In front of the bleeding an area of hypodensity was seen to the level of Reil's insula (fig 2). At 6 months both the ultrasound scan and neuromotor development remained within normal limits.

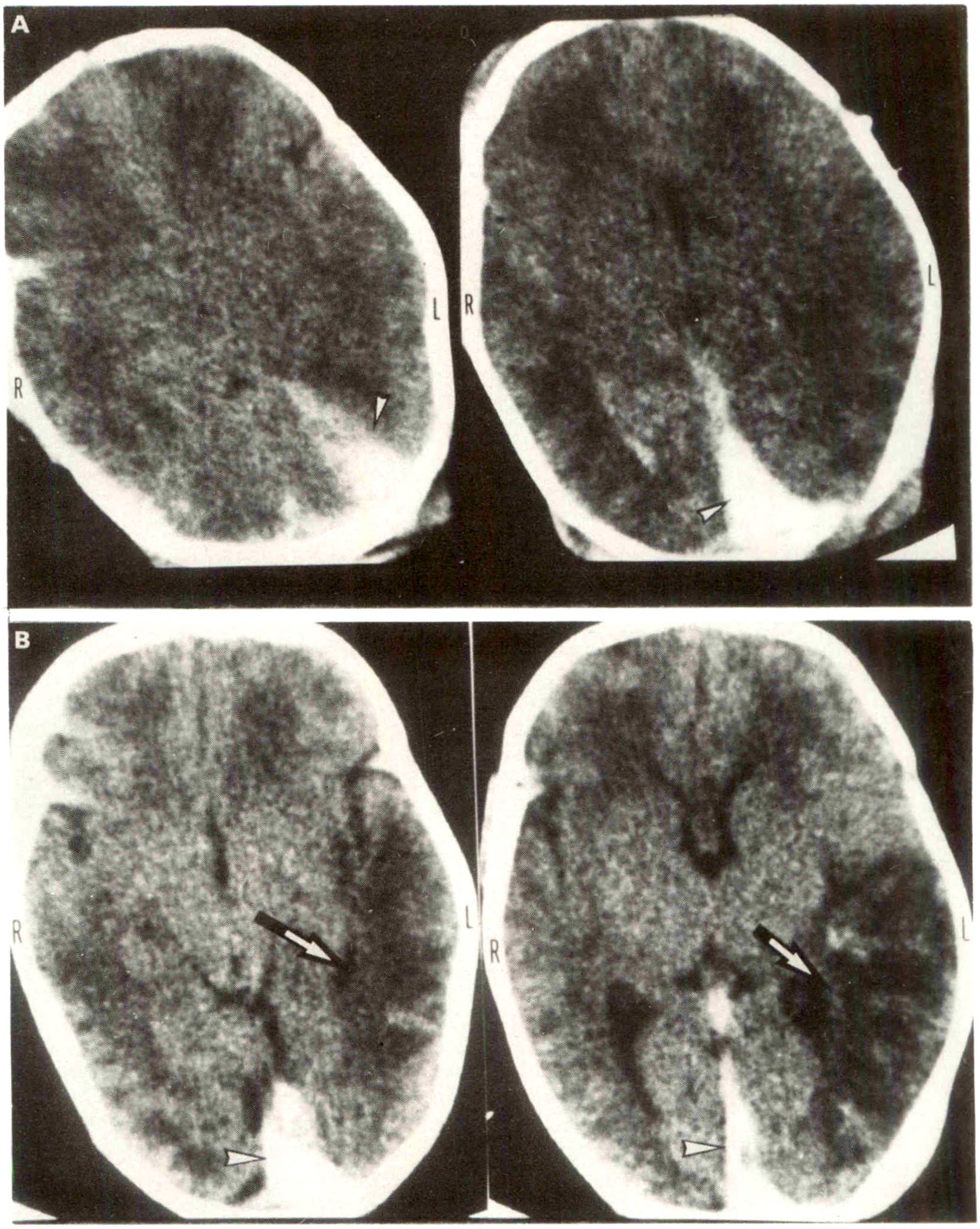


Figure 1 Case 1, uncontrasted computed tomograms. (A) On day 2, a supratentorial haemorrhage is visible mainly above the left tentorial leaflet and within the posterior interhemispheric fissure (arrowheads). (B) On day 8, there are residual haemorrhagic densities (arrowheads) and there is a hypodense territory around the left middle cerebral artery (arrows).

CASE 3

This girl was delivered by breech at term. The second stage took 26 minutes. Apgar scores were 9 and 10 at 1 and 5 minutes. She weighed 3010 g at birth. Six hours later her fontanelle became tense and she developed general seizures, hypotonia, and lethargy. Her cry was high pitched. Endotracheal ventilatory support was given for recurrent apnoea with gasping and a fixed bradycardia. Opisthotonus, Battle's sign (retroauricular cephalhaematoma), and a left facial palsy were recorded upon admission. Lumbar cerebrospinal fluid was bloodstained. An emergency computed tomogram demonstrated bilateral peritentorial bleeding and left basal convexity subdural haemorrhage. The girl died on day 3 with intractable seizures. Necropsy revealed infarction in the parietal region of the left middle cerebral artery.

CASE 4

This firstborn boy was delivered by breech at 37 weeks of gestation. After a short first stage of labour, the breech passed easily but considerable difficulty was met with while freeing the arms and delivering the head. His Apgar scores were 1 and 2 at 1 and 5 minutes. He weighed 1340 g at birth. Several hours later he was referred with cyanosis, apnoea, clonic seizures, and hyponatraemia. Intracranial hypertension remained present for several days. The computed tomogram on day 5 showed bilateral basal convexity subdural haemorrhage, most pronounced on the right; both temporal lobes seemed hypodense especially medially (fig 3). After recovering from the acute episode he needed plication of the right diaphragm for permanent phrenic nerve palsy and orthopaedic treatment of a fractured right humerus as well as a dislocated left

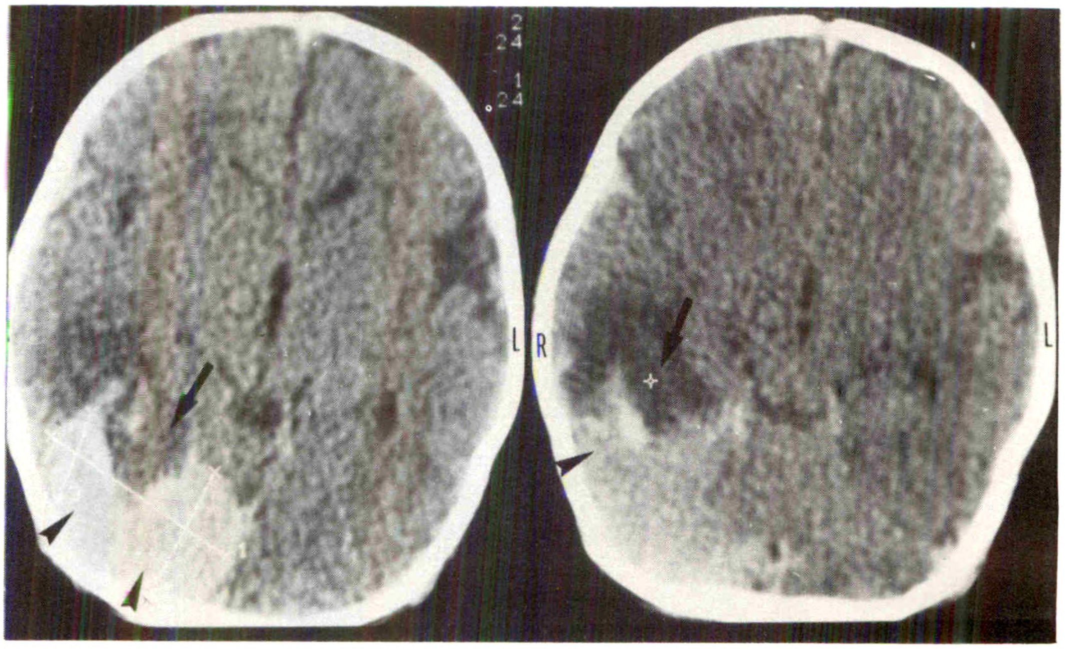


Figure 2 Case 2, uncontrasted computed tomograms on day 6 showing combined subdural and intracerebral haemorrhage in the right temporal region (arrowheads) and white matter hypodensity of part of the temporal lobe (arrows).

shoulder. On follow up at 2 months a control computed tomogram demonstrated bilateral occipital lobe infarction. This boy developed spastic tetraplegia and cortical blindness.

CASE 5

This girl was delivered at 42 weeks of gestation by caesarean section because of occipitoposterior presentation, cephalopelvic disproportion, and decelerations in the second stage. Her Apgar score was 8 and 10 at 1 and 5 minutes. Birth weight was 3500 g. Six hours later she presented with left focal seizures, convulsive apnoea, a shrill cry, and hypotonia. Palpable separation between the right and left frontal bones was noticed. An ultrasound scan revealed increased densities in the right cerebral parenchyma while the computed tomogram showed diffuse subarachnoid haemorrhage and hypodensity of the occipitotemporal cerebral parenchyma. Focal disturbance of the EEG was present over the right hemisphere. Subtle seizures persisted for two weeks, as well as skew eye deviations and a left hemiparalysis. Her fundi were normal. The computed tomogram at 3 months showed the sequelae of infarction within the territory of the right posterior cerebral artery (fig 4). At 2 years neuromotor development was within normal limits.

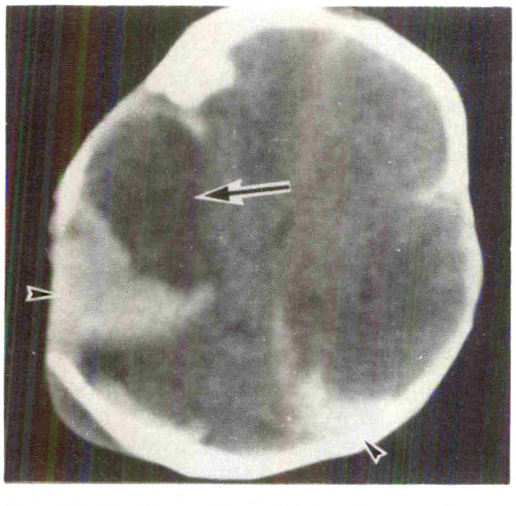


Figure 3 Case 4, uncontrasted computed tomogram on day 5 showing bilateral basal convexity subdural haemorrhage, mainly on the right (arrowheads) with associated temporal lobe hypodensity (arrow).

CASE 6

This firstborn boy was delivered by breech at 39 weeks of gestation. Fundal pressure was exerted to deliver the aftercoming head. Apgar scores were 1 and 4 at 1 and 5 minutes respectively. Birth weight was 2350 g. In the course of the first day he became pale, hypotonic, and lethargic and was referred with a tense fontanelle and because of suspected extracerebral bleeding shown on a computed tomogram. Neither seizures nor anisocoria were observed. Heart rate was steady at around 120 beats/minute. A lentiform density on ultrasound and computed tomography was pathognomonic of epidural haematoma (fig 5). There appeared to be a linear fracture of the right parietal bone. Hypodensity of the ipsilateral occipitotemporal cerebral brain tissue and increase of intracranial pressure prompted neurosurgical intervention on day 3. Under local anaesthesia the haematoma, partially liquefied, was aspirated through a dural incision via the lambdoid suture. In the immediate postoperative period, the fontanelle lost its tension and both the midline shift and the parenchymal hypoperfusion disappeared. A residual epidural hygroma resorbed over the ensuing days. Within the first months of life clinical suspicion of Prader–Willi syndrome was confirmed by a typical deletion of chromosome 15.

CASE 7

This girl, only known to us by her computed tomograms and a limited clinical history, was

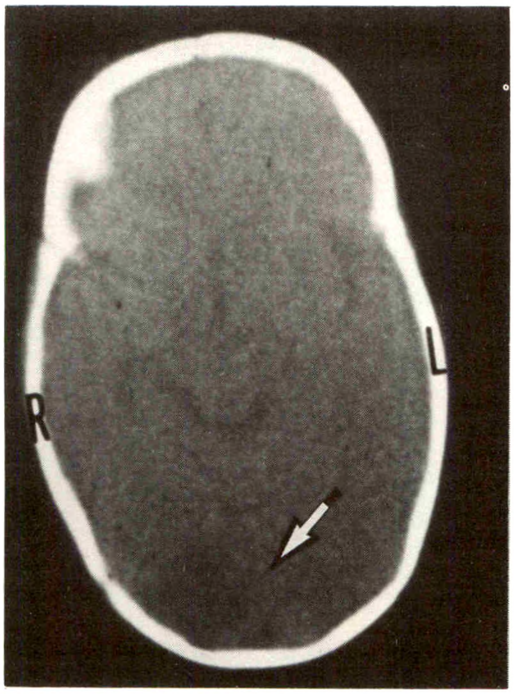


Figure 4 Case 5, uncontrasted computed tomogram at 3 months showing focal tissue loss within the territory of the right posterior cerebral artery.

born at term with unspecified difficult vacuum extraction. She presented with subaponeurotic bleeding and soft neurological signs. Within the neonatal period conventional radiographs and computed tomograms showed bilateral parietal bone fractures (with depression of the anterior fracture margins on the right), subarachnoid and falcial bleeding, a small convexity subdural haematoma on the right, and multifocal hyperdensity of the right postinsular (sub)cortex suggesting cerebral contusion (fig 6A). At the age of 14 months a left spastic hemiplegia was observed. She had a triangular brain defect within the posterior territory of the right middle cerebral artery (fig 6B).

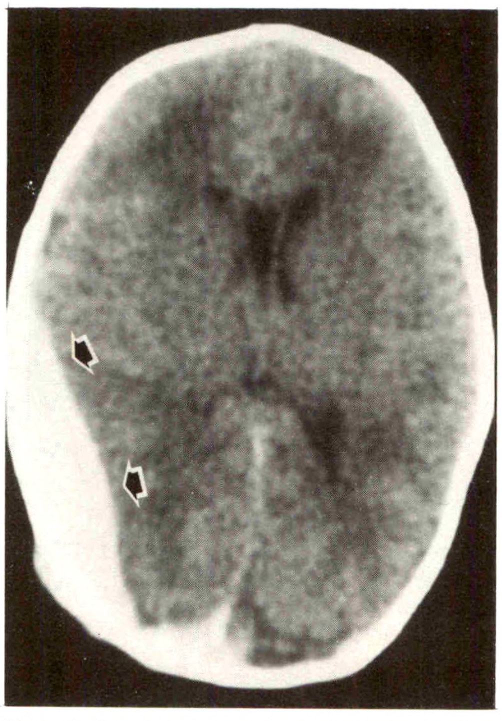


Figure 5 Case 6, uncontrasted computed tomogram on day 2 showing large lentiform density along the right dural membrane.

Discussion

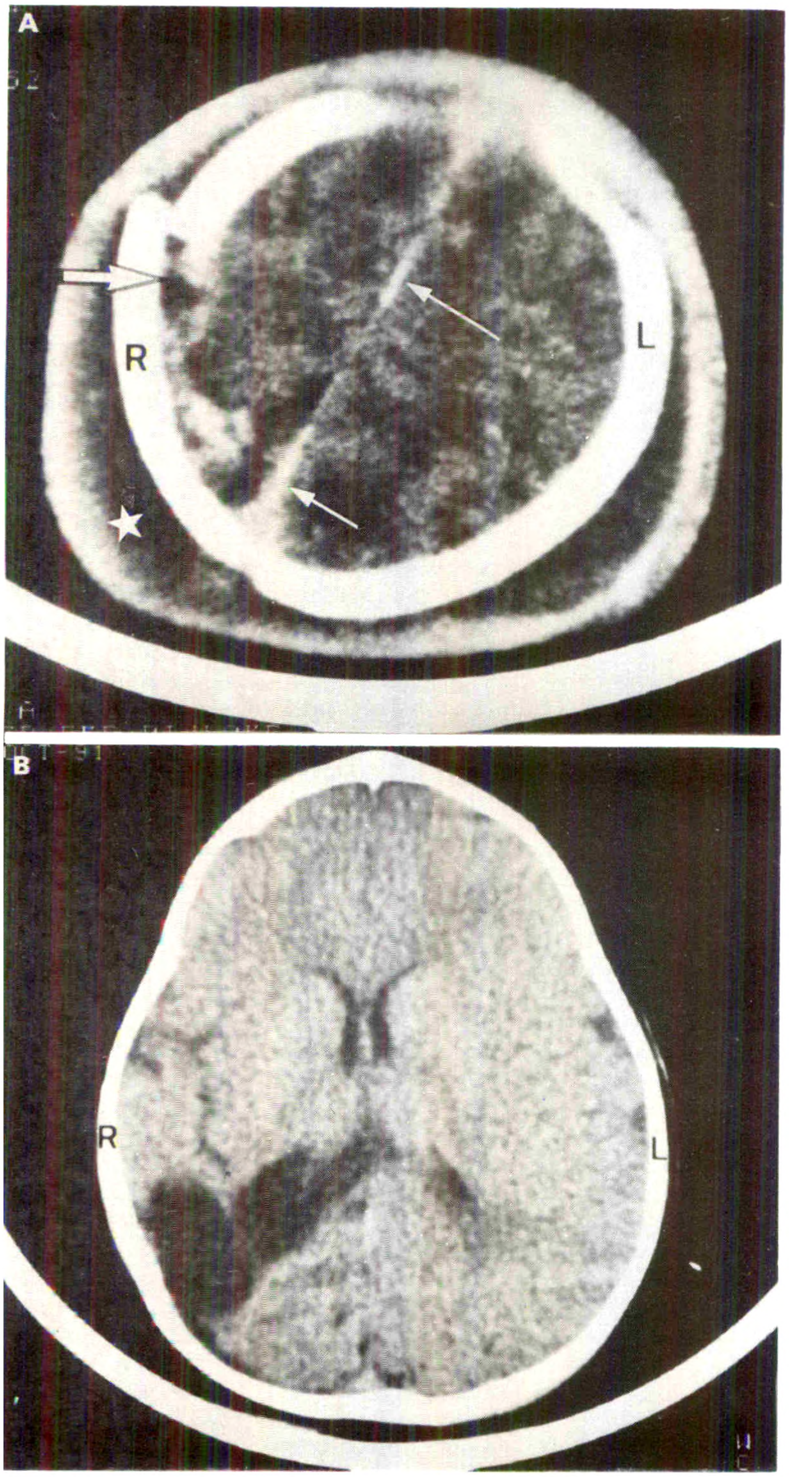
Ischaemia within the regions supplied by the middle or posterior cerebral artery after mechanical trauma at birth has been reported in about 10 living patients. This association was convincingly introduced by Remillard *et al* in studying eight patients, aged 3 to 39 years, with temporal lobe epilepsy, homonymous hemianopsia or quadrantanopsia, and enlargement of the occipitotemporal lateral ventricle area.[16] The difficult births in five of these patients, one with forceps extraction, and the related angiographic demonstration of occlusion of the posterior cerebral artery or its calcarine and occipitoparietal branches, were very suggestive of a perinatal insult.

The link between mechanically difficult delivery and temporal lobe epilepsy was established several years later in a report on two boys delivered at full term with difficult vacuum extraction, presenting with psychomotor seizures at 4 and 10 years respectively.[15] The first one presented with acute neonatal supratentorial convexity subdural bleeding, whereas the second had a growing 'cephalhaematoma'. The computed tomogram at follow up documented a right occipital porencephalic lesion in both. The authors re-emphasised that in older children and adults temporal lobe herniation through the tentorial aperture had been shown to occlude the posterior cerebral artery and induce incisural sclerosis.[18 19]

A different and well documented neonatal stretch injury of the middle cerebral artery was reported in a full term girl delivered by caesarean section after a failed high forceps extraction attempt.[17] Lumbar cerebrospinal fluid in this child was bloodstained, while a computed tomogram suggested falcial bleeding and brain oedema. She died on day 4. Postmortem examination revealed several foci of subarachnoid haemorrhage, a soft and swollen right cerebrum in the distribution zone of the middle cerebral artery with central haemorrhagic necrosis, right uncal herniation and bilateral cerebellar coning. The middle cerebral artery carried a thrombus 0·8 cm from its origin. Light and electron microscopy showed disruption of the lamina elastica interna near the vessel occlusion. It was the author's conviction that this lesion followed stretching of the vessel during difficult delivery.

The growing interest in perinatal arterial cerebral stroke encouraged description, during the eighties, of at least six additional instances where birth trauma may have generated this event. They presented with unilateral middle cerebral artery occlusion after forceps delivery,[5 12 20 21] except for one with precipitate vaginal birth.[22] Several authors mentioned intact neurological survival.[5 12] Supratentorial subdural bleeding (on magnetic resonance imaging) was referred to only in one report.[23]

In his monograph on cranial birth trauma up to 1964, Schwartz showed limited interest



igure 6 Case 7, uncontrasted computed tomograms. (A) On day 2, showing extensive ubgaleal bleeding (star), subarachnoid and intradural haemorrhage (small arrows) and onvexity subdural haemorrhage (large arrow) underneath a depressed fracture margin. B) At 14 months, showing a triangular defect in the posterior region of the right middle erebral artery.

in arterial cerebral injury.[13] Direct damage to the middle meningeal artery and associated epidural bleeding after forceps delivery were already documented and laceration of the basilar artery had been recognised in a preterm infant.[24] A genuine milestone observation was made by Yates in 1959.[14] Searching for traumatic neck lesions in 60 perinatal deaths this author recorded 24 neonates with haemorrhage in the adventitial coat of one or both vertebral arteries. These haemorrhages, sometimes up to 1 cm in length, occluded part or whole of the vessel lumen. Some of them arose from torn arterial branches near their origin. Obstruction of one vertebral artery was sufficient to produce bilateral lesions in the brain stem, cerebellum, and occipitotemporal cerebral cortex.

We believe that in the present report cases 4, 5, and 6 fit the mechanism of supratentorial intracranial hypertension leading to uncal herniation and thus causing occlusion of the ipsilateral posterior cerebral artery.[15] [16] The first three cases suggest the existence of another mechanism: basal convexity subdural bleeding leading to occlusion of the ipsilateral middle cerebral artery or its branches. This vessel obstruction might follow stretch injury and subsequent thrombosis,[17] direct compression by the space occupying haematoma, or arterial embolism. Vasospasm due to the presence of surrounding subarachnoid haemorrhage, as in adults, may well be another mode of genesis.[25] In favour of this hypothesis is the observation in our first child of the absence of ischaemia on day 2 and its subsequent appearance on day 8. The necessity of performing a scan in the second week of life to detect arterial cerebral stroke in neonates with seizures, is already recognised.[5] Attenuation of affected zones on an uncontrasted computed tomogram normally presents within hours after occlusion, rendering unlikely the hypothesis of direct arterial damage in our first patient.[26] Experimental work supports the idea of erythrocyte induced perihaemorrhagic vasoconstriction of isolated cat middle cerebral arteries.[27] In addition, spasm of the middle cerebral artery has been reported in older children with head and neck injury.[28]

The absence of left predilection, currently observed in neonatal stroke in general, in this series of trauma related cerebral infarctions is

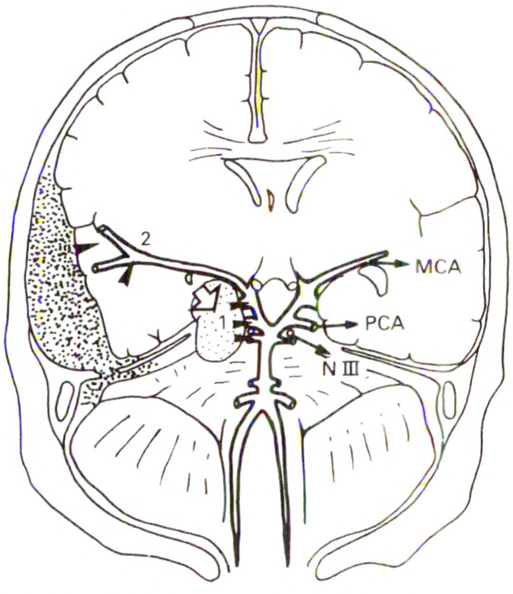


Figure 7 Schematic drawing of two mechanisms generating post-traumatic arterial cerebral occlusion. (1) Uncal herniation (large open arrow) leading to compression (arrowheads) of the posterior cerebral artery (PCA), middle cerebral artery (MCA) and/or oculomotor nerve (N III). (2) Basal convexity subdural haemorrhage leading to compressions and/or spasm of the middle cerebral artery or its branches (arrows).

compatible with a local and not an embolic phenomenon.[29] Whatever the underlying mechanism, both the posterior and middle cerebral artery are vulnerable to occlusion after peritentorial subdural bleeding (fig 7). Whereas an isolated subdural haematoma often leaves no neurological sequelae, its association with arterial hypoperfusion predisposes to cerebral palsy if the affected region becomes ischaemic as happened to four of the six survivors in our series.

In case 7 arterial occlusion of a posterior branch of the middle cerebral artery might have been brought about by compression from swollen brain parenchyma, in addition to the above mentioned mechanisms. Of some importance may be the rarity of these lesions after breech delivery (only three in 17 reviewed cases) and the possibility of their occurrence after vacuum as well as forceps extraction, supporting the proposed hypothesis of supratentorial injury as an initiator.

In conclusion, we suggest that compression and/or spasm of the middle cerebral artery or its branches, as a consequence of basal convexity subdural haemorrhage or parietal cerebral contusion, is one cause of traumatic neonatal arterial cerebral stroke.

We are indebted to Dr S van Werveke, Dr V de Telder, Dr L Callewaert, and Dr P Jeannin for entrusting to us the care of their special birth trauma cases and to Eric and Will for their photographic skills.

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Archives of Disease in Childhood 1992; **67**: 846–850

Athetoid cerebral palsy with cysts in the putamen after hypoxic-ischaemic encephalopathy

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Abstract

Three cases of athetoid cerebral palsy after hypoxic-ischaemic encephalopathy (HIE) are reported. All three neonates had haemorrhagic lesions in the basal ganglia and thalami on magnetic resonance imaging (MRI). Prior cranial ultrasound had detected the lesions in only two cases. In all three children athetoid movements began within the first year of life. Follow up MRI scans showed bilateral symmetrical cystic lesions in the posterior putamen. Although haemorrhagic lesions within the basal ganglia are a common MRI finding in neonates with HIE, few of these babies develop athetoid cerebral palsy. We believe this to be the first report of discrete cystic lesions found in the basal ganglia of children with athetoid cerebral palsy.

The relationship between neonatal asphyxia and lesions in the thalamus and basal ganglia has been recognised for many years. The appearance of status marmoratus was first described in 1911,[1] but it was not until 1950 that an association with this lesion and a history of birth asphyxia was suggested.[2] In recent years, lesions in the thalami have been described using ultrasound in neonates with severe hypoxic-ischaemic encephalopathy (HIE)[3-5] and the more sensitive techniques of magnetic resonance imaging (MRI) have shown haemorrhagic lesions within thalami and basal ganglia in babies with even mild HIE (JM Pennock *et al*, personal observation). However, to date there have been no published reports of clinical or radiological follow up on infants with these thalamic lesions. In this paper we describe three infants with thalamic and basal ganglia lesions on neonatal MRI scans who have developed cystic lesions in the putamen on follow up images. All three infants now have athetoid cerebral palsy.

Patients and methods

These infants were part of our prospective study of babies with HIE and were assessed with the following techniques: regular neurological examination, using a standardised proforma,[6] regular cranial ultrasound, cerebral Doppler blood flow studies, continuous electroencephalographic monitoring, computed tomography, and MRI. On follow up visits each baby had a neurological examination, cranial ultrasound until closure of the anterior fontanelle, and Griffiths's developmental assessment. Follow up MRI scans were performed when possible.

Cranial ultrasound was performed with an Advanced Technical Laboratories Ultramark III sector scanner using both 5 mHz and 7·5 mHz transducers. A Picker 0·15 Tesla magnet was used for MRI. Imaging was performed using both T1 weighted inversion recovery and T2 weighted partial saturation sequences. The parameters used during the neonatal period and infancy have been described elsewhere.[7]

All infants over 3 months of age were sedated with 80 mg/kg of chloral hydrate. Younger babies were imaged while asleep and after a feed. All patients were monitored with electrocardiography and an apnoea alarm.

Results

In our current series of 25 infants with HIE who have shown haemorrhagic lesions in the basal ganglia and thalamus on neonatal MRI scans only four have developed cerebral palsy with athetoid movements. In the three with appropriate follow up scans we have demonstrated bilateral cystic lesions within the posterior part of the putamen. The fourth child has not had repeat imaging using the same sequence. Clinical details of each infant with lesions in the putamen and details of their ultrasound, computed tomograms, and MRI scans are given below and in tables 1 and 2.

Table 1 Clinical details in neonatal period

Case No	*Delivery*	*Apgar score (1,5 min)*	*EEG*	*Cranial ultrasound*	*Discharge examination*
1	Spontaneous vaginal delivery	1,1	Discontinuous activity, low amplitude activity	7·5mHz only, periventricular densities	2 Weeks, jittery tremors, ↑ arm tone, feeding well
2	Emergency caesarean section	1,1	Discontinuous activity, low amplitude activity, seizures	Slit-like ventricles, thalamic densities	12 Days, irritable asymmetrical tone, feeding well
3	Emergency caesarean section	3,7	Low amplitude activity	Featureless, thalamic densities	12 Days, ↑ tone, adducted thumb feeding well

EEG=electroencephalogram.

Table 2 Clinical details on follow up

Case No	*6 Weeks*	*1 Year*	*Diagnosis*
1	Jittery, irritable, ↑ arm tone	Hypertonic, drooling, athetoid movements	Athetoid cerebral palsy
2	Irritable, ↑ tone	Dystonia, athetoid movements, mouth open++	Athetoid cerebral palsy
3	Irritable, tremors, fisting ↑ tone	Infantile spasms, athetoid movements, drooling, tight hip adductors	Athetoid cerebral palsy

CASE REPORTS

Case 1

A boy, weighing 4200 g, was born to healthy West Indian parents. A fetal bradycardia was recorded for 20 minutes before the delivery when the cord was found tightly around the neck. The baby was intubated but spontaneous respiration was not established for 20 minutes. A prolonged convulsion occurred at 6 hours of age, despite 35 mg phenobarbitone given prophylactically by the referring hospital. A further dose of phenobarbitone was

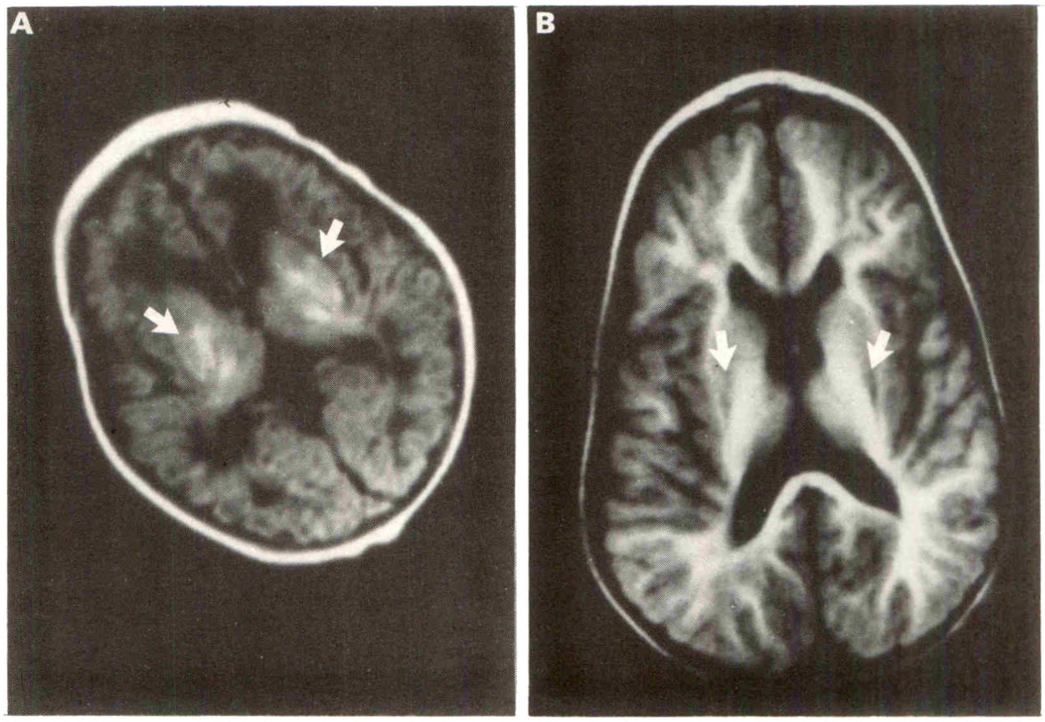

Figure 1(A) Haemorrhagic lesions (arrows) in the basal ganglia and thalami on inversion recovery sequence. (B) Cystic lesions (arrows) in the posterior putamen on inversion recovery sequence.

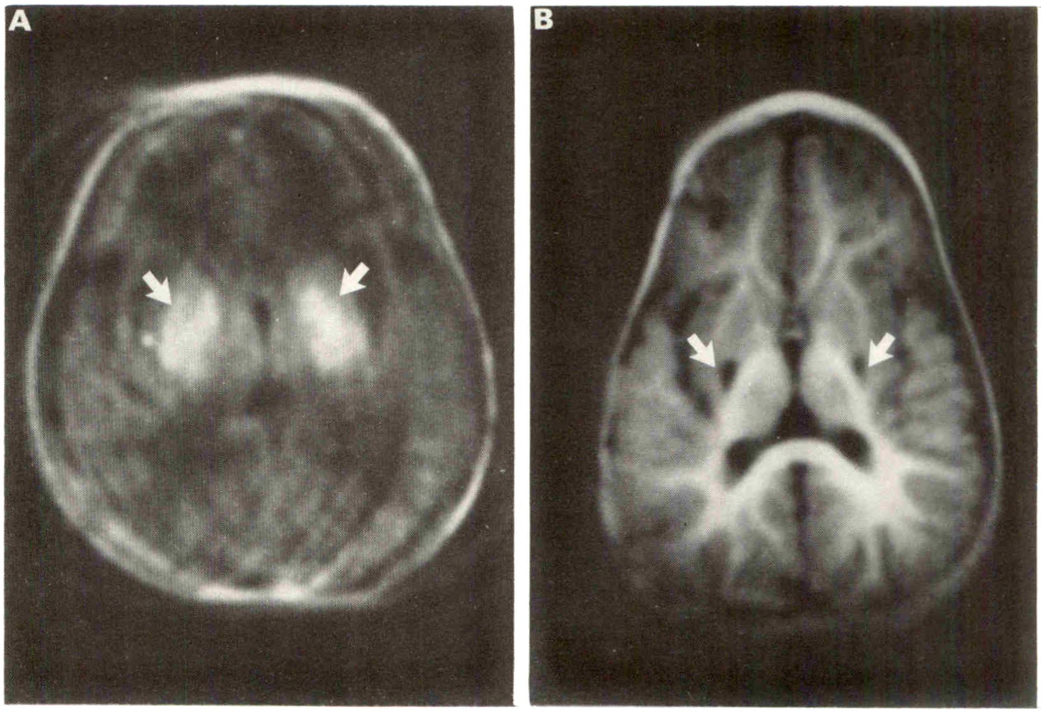

Figure 2(A) Haemorrhagic lesions (arrows) in the basal ganglia and thalami on inversion recovery sequence (some movement artefact). (B) Cystic lesions (arrows) in the posterior putamen on inversion recovery sequence.

given and a maintenance dose given for one week. There were no recorded episodes of hypoglycaemia, polycythaemia, acidosis, or hypocapnia. The maximum serum bilirubin concentration was 52 µmol/l. A computed tomogram on day 11 showed decreased attenuation in the periventricular areas but no lesions within the basal ganglia. MRI inversion recovery sequence on day 9 showed patchy areas of high signal intensity within the thalamus and basal ganglia, consistent with haemorrhage or haemorrhagic infarction (fig 1A).

A repeat MRI scan at 22 months showed bilateral symmetrical low signal intensity lesions in the putamen on inversion recovery sequence with a corresponding high signal intensity on partial saturation images (fig 1B). This is consistent with cyst formation. No other lesions were seen and myelination was within normal limits. At this stage head circumference was on the 10th centile and the weight <3rd centile.

Case 2

A girl, weighing 2600 g, was born to a white mother and African father. Labour was induced for maternal diabetes and delivery was by emergency caesarean section for fetal distress and meconium stained liquor. An initial umbilical arterial blood gas showed a mixed acidosis with a pH of 7·07. A chest radiograph was compatible with meconium aspiration. Convulsions were noted on day 3. These were treated with two doses of phenobarbitone and ceased after 24 hours. Early Doppler blood flow studies showed a pulsatility index of <0·55. Maximum serum bilirubin concentration was 42 µmol/l and there were no episodes of hypoglycaemia, polycythaemia, or hypocapnia.

Inversion recovery sequences on MRI at 10 days showed high signal areas in the basal ganglia and thalami (fig 2A). Repeat MRI at 13 months showed bilateral symmetrical low signal areas in the putamen on inversion recovery sequences with a corresponding high signal on partial saturation images (fig 2B). No other lesions were seen and myelination was within normal limits. At the time of writing her head circumference has fallen to the 3rd centile but her weight has also fallen to below the 3rd.

Case 3

A boy, weighing 3400 g, was born to healthy Asian parents. Delivery was by emergency caesarean section for fetal distress after failed Kielland's forceps delivery and failed vacuum extraction. The baby was intubated after delivery and ventilated for 45 minutes. A capillary blood gas at 1 hour of age showed a pH of 7·1. Convulsions were noted at 5 hours of age and continued for 48 hours despite anticonvulsant treatment, necessitating a period of reventilation. There were no recorded episodes of hypoglycaemia or polycythaemia and there was no jaundice. A computed tomogram at 10 days showed generalised low attenuation of the white matter, but no lesions were seen within the thalami or basal ganglia. An MRI inversion recovery sequence showed bilateral high signal areas in the thalami and basal ganglia at 8 days (fig 3A). A repeat MRI scan at 17 months showed bilateral symmetrical low signal areas in the putamen on inversion recovery sequences with a corresponding high signal intensity on partial saturation images (fig 3B). No other lesions were seen and myelination was within normal limits. His head circumference was on the 10th centile and his weight was below the 3rd centile.

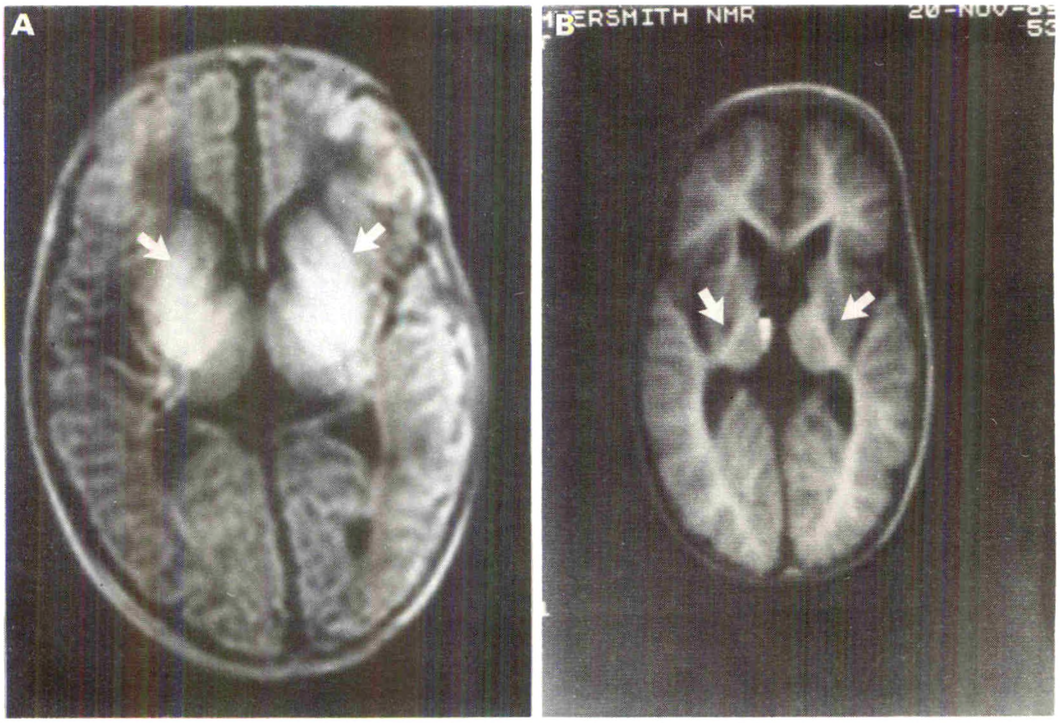

Figure 3(A) Haemorrhagic lesions (arrows) in the basal ganglia and thalami on inversion recovery sequence. (B) Cystic lesions (arrows) in the posterior putamen on inversion recovery sequence.

Discussion

The development of athetoid cerebral palsy has been associated with two particular neonatal conditions, kernicterus and HIE.[8] Pathological lesions in the basal ganglia and thalamus were first documented over 40 years ago both in children with a history of kernicterus[9] and in those with birth asphyxia.[10 11] With improvements in perinatal care kernicterus has become an unusual cause of athetoid cerebral palsy in the developed world,[12] and in children presenting with athetoid cerebral palsy there is often now a history of HIE. In contrast to the detailed descriptions of kernicterus the literature relating to the development of athetoid cerebral palsy after HIE is limited. In children with HIE who then develop athetoid cerebral palsy most studies are retrospective with poor documentation of clinical state and investigations in the neonatal period.[8 13 14]

We are unsure whether the neonatal course of our infants is typical of babies who go on to develop athetoid cerebral palsy after HIE. We are, however, able to show that the neonatal findings in our babies were very different from babies who develop athetoid cerebral palsy following kernicterus. Since the term kernicterus was coined by Schmorl in 1903[15] there have been many descriptions of the early and later clinical course of infants with this disorder.[8 16 17] After an initial period of hypertonia with opisthotonus the infant becomes hypotonic. This lasts for a variable time but athetoid movements may not appear for several years. In contrast our three babies all showed some hypotonia in the first few days but once anticonvulsants had been discontinued the babies all showed varying forms of hypertonia and were excessively irritable with persistent tremulous and jittery movements. Despite these neurological findings all three babies were ready for discharge home by the end of the second week of life. Of interest is that although severely asphyxiated babies often have prolonged problems in establishing normal feeding, all our babies were feeding well by day 10.

After the neonatal period infants with HIE are reported as being hypotonic for a variable period of time, with persistence of primitive reflexes.[13 18] The onset of athetoid movements is usually after the first year of life. Once the condition is established the tone may be hypotonic, hypertonic, or fluctuating in nature. Children who develop athetoid movements before the age of 1 year are thought to be less severely affected.[18] Our babies do not appear to have followed this 'classical' clinical course. After the neonatal period they were hypertonic with jittery and tremulous movements for several months. Persistent mouth opening and/or dribbling was noted early on and all had developed abnormal movements by the end of the first year. However, in contrast to previous reports none could be described as having only mild cerebral palsy.[18] In all three children the head circumference remained proportional to the weight and there was no evidence of cortical atrophy on MRI. Myelination was also described as within normal limits in all three children. Maintenance of good head growth may provide an early clue that an infant with abnormal tone pattern will develop athetoid cerebral palsy as opposed to a spastic quadriplegia.

It is well recognised that the basal ganglia and thalamus are particularly vulnerable to hypoxic-ischaemic damage,[19] but we have been unable to find any reports of athetoid cerebral palsy occurring in an infant with a thalamic/basal ganglia lesion documented in the neonatal period. To date most reports of these lesions have used cranial ultrasound or computed tomography.[3 4 20 21] Two of our patients had computed tomography performed and no lesions were seen in this area. However, the scans were not performed during the first week of life and any haemorrhage may have become isodense with the surrounding tissue. When the lesions were identified using cranial ultrasound a 5 mHz scanning head was needed. It may be that when haemorrhage in these areas is documented with an imaging technique that is less sensitive than MRI it is so severe and/or extensive that the clinical outcome has often been death.[4 20 21] It is of interest that in our current series of 25 infants with lesions seen at this time only four have developed athetoid movements. In three of these who have had appropriate follow up images we have shown very isolated and apparently identical lesions. In addition to our three reported babies, two out of the 12 children who had follow up scans had cysts in the lentiform nucleus. One of these had small bilateral cysts in the medial putamen, but an otherwise normal scan, and is now developmentally normal. The second child has widespread damage throughout the basal ganglia and thalami with bilateral cysts in the globus pallidum and has developed a severe spastic quadriplegia. From these cases it would appear that damage to a very specific area of the putamen may be responsible for the development of athetosis. However, as all three children had more extensive lesions within this area in the neonatal period these may be contributing to the development of the athetosis.

Athetoid cerebral palsy has been reported in children with a wide variety and combination of lesions within the basal ganglia and thalamus.[8] It is not known whether a specific site of damage, or combination of sites, is responsible for the disorder. In addition the disturbance or neurotransmitter imbalance that leads to athetosis is still not understood.[22] Information on the site of damage and the neurotransmitter imbalance in athetoid cerebral palsy can only be established by further research. Studies using techniques such as MRI, magnetic resonance and spectroscopy, and positron emission tomography in children with established athetosis may provide the answers.

We would like to thank Professor Graeme Bydder, department of magnetic resonance imaging, for his help in interpreting the images. Dr Mary Rutherford is supported by The Spastics Society.

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Archives of Disease in Childhood 1992; **67**: 851–854

Regional cerebral blood flow velocity changes after indomethacin infusion in preterm infants

N C Austin, P W Pairaudeau, T K Hames, M A Hall

Abstract

Cerebral blood flow velocity was assessed during infusion of indomethacin over 30 minutes. Eleven preterm infants with symptomatic patent ductus arteriosus were studied on 12 occasions. Indomethacin infusion was associated with a significant reduction in time averaged mean velocity (TAMV), peak systolic velocity (PSV), and end diastolic velocity in both the anterior cerebral artery and middle cerebral artery. The fall in the TAMV and PSV was gradual with maximal change 30–40 minutes after the start of the infusion. It was concluded that administration of indomethacin by slow infusion produces haemodynamic alterations to the cerebral circulation comparable in magnitude with changes described with bolus administration. Indomethacin remains a useful and effective treatment for patent ductus arteriosus in preterm infants, but should continue to be used with caution.

Indomethacin is widely used in the treatment of symptomatic patent ductus arteriosus in preterm infants. The effect of indomethacin treatment on the cerebral circulation of the neonate has been assessed by Doppler ultrasound[1–7] and near infrared spectroscopy[8] in recent years. Most investigators[1–6] have studied the effect of rapid (up to five minutes) injection of indomethacin on blood flow velocity in the anterior cerebral artery (ACA) or internal carotid artery (ICA). These studies have shown a rapid decline in mean blood flow velocity by up to 60–75% of pretreatment levels within five minutes of the completion of the injection. A decrease in both the peak systolic and diastolic velocities accounted for the fall in mean blood flow velocity. The findings of one study,[7] using 'blind' isonation of the ACA with continuous wave Doppler, suggested that infusion of indomethacin over 20 minutes avoids the fall in cerebral blood flow velocity (CBFV) seen with more rapid administration. However, a more recent study using near infrared spectroscopy[8] did not confirm these findings and failed to show a difference in the fall in total cerebral blood flow when injection of indomethacin over five minutes was compared with slow infusion (20–30 minutes).

To date there have been no studies of the effects of indomethacin on different regional areas of the cerebral circulation of human infants. In the following report both the anterior and the middle cerebral arteries were studied using duplex scanning, to determine whether prolonged infusion (over 30 minutes) of indomethacin was associated with changes in CBFV and if so whether regional differences in CBFV could be demonstrated.

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Accepted 25 November 1991

Method

Eleven infants with echocardiographic confirmation of patent ductus arteriosus were selected for indomethacin treatment on clinical grounds. All cases had failed to respond to a trial of 48 hours of fluid restriction (120 ml/kg). One infant received two courses of indomethacin 21 days apart. Indomethacin was given via a peripheral vein in a dose of 0·2 mg/kg/dose 12 hourly for three doses. The dose was diluted in 1 ml of sterile water and infused over 30 minutes. The drug infusion system was connected via a butterfly needle close to the cannula site in the vein to ensure complete drug administration over the 30 minutes. Only first dose studies for each course are reported.

Arterial or capillary carbon dioxide concentrations, blood pressure, and fluid intake were measured in the 24 hours before indomethacin administration. During the infusion heart rate, transcutaneous oxygen and carbon dioxide levels (if available), and blood pressure were monitored.

Two vessels were insonated using a Hewlett Packard duplex scanner with a 5 MHz short focus probe and 100 Hz wall thump filter. Measurements were recorded on video tape for later analysis. The ACA was insonated, via the fontanelle, as it runs up toward the corpus callosum. The angle between the probe and artery could be visualised and the probe position was adjusted so that the angle of insonation at the time of study, before data collection, was less than or equal to 10 degrees for which no correction was made (a 3% error). The middle cerebral artery (MCA) was insonated transcranially through the temporal bone as the vessel leaves the circle of Willis and again the angle was maintained close to zero degrees in all cases. The depth of the probe from the skin surface was recorded and an attempt made to keep this constant; alternatively the closest strongest signal was used.

Echocardiographic assessment of left ventricle dimensions, left atrial to aortic ratio, and pulmonary artery and descending aorta Doppler velocities were performed before treatment and one hour later.

Vasoscan (Oxford Sonocaid) was used to provide off line spectral analysis of the taped data. The parameters measured were peak systolic velocity (PSV), end diastolic velocity (EDV), and time averaged mean velocity (TAMV) calculated from the instantaneous mean velocity. Doppler examinations were carried out in the 10 minutes before infusion, at 5 minutes and at 10 minute intervals until 60 minutes, and in some babies up to 2 hours, after the start of indomethacin infusion. At least three segments of 3 to 9 seconds' duration were averaged to obtain the mean TAMV, PSV, and EDV.

The mean pretreatment value for TAMV, PSV, and EDV were compared with the maximum change or nadir in the fall observed and the change at 60 minutes. A paired *t* test was used to detect a significant difference. Results are shown as mean (SD).

The coefficient of variation (SD as a percentage of the mean) was calculated for the pretreatment values for TAMV, PSV, and EDV for each infant; a percentage change greater than 2 SD from the group mean should be significant at the 95% confidence limits.

Six preterm infants, without echocardiographic evidence of a patent ductus arteriosus, were assessed for at least 30 minutes using a similar protocol and handling as in the study to assess whether any changes could be attributed to the study procedure.

Parental consent and ethics committee approval were obtained.

Results

The median birth weight was 1030 g (range 680–1850), median gestation at birth 27 weeks (range 24–32 weeks), and median postnatal age at treatment 9 days (7–30). Twelve studies in 11 infants were analysed. Eight babies were receiving artificial ventilation at the time of the first dose. The median arterial carbon dioxide tension pretreatment was 6·1 kPa (range 4·1–7·4). The median total fluid intake in the 24 hours before treatment was 133·5 ml/kg (range 96–190) and the median haemoglobin concentration 118 g/l (range 93–159). There was no correlation between the carbon dioxide level, fluid intake, or haemoglobin concentration and the changes in the TAMV, PSV, or EDV. Five of the infants had continuous blood pressure monitoring and transcutaneous measurement of oxygen and carbon dioxide. No significant changes were recorded. In five others the measurements were intermittent.

An average of 4·25 segments of the scan, each of 6·7 seconds' duration or an average of 70 cardiac cycles, were analysed per measurement.

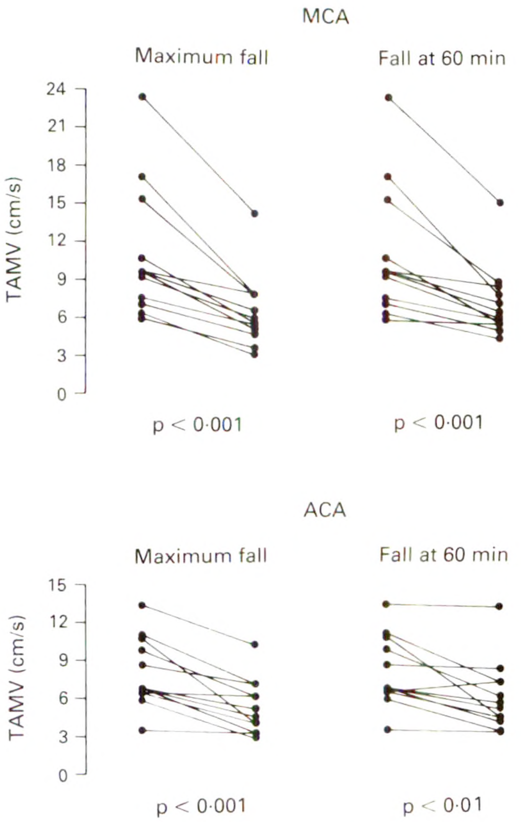

Figure 1 Change in the TAMV after indomethacin infusion.

Table 1 Statistical analysis of the TAMV

Site	*Time*	*Mean velocity change*		*95% Confidence interval (cm/s)*	*p Value*
		cm/s	*%*		
MCA	Maximum change	4·36	−40·0	2·91 to 5·817	<0·001
	60 minutes	3·65	−31·6	2·03 to 5·26	<0·001
ACA	Maximum change	2·70	−32·9	1·67 to 3·74	<0·001
	60 minutes	1·98	−24·0	0·72 to 3·24	<0·01

Table 1 shows that the maximum fall in TAMV was −40·0% in the MCA and −32·9% in the ACA; this occurred at 36·5 and 31·5 minutes (median) after the start of indomethacin infusion respectively. These values were compared with pretreatment recordings to determine whether a significant change had occurred. The absolute changes in the TAMV for each artery are shown at maximum fall and at 60 minutes in figure 1. The maximum fall was significant (p<0·001) in both vessels and was more pronounced in the MCA (p<0·001) than the ACA (p<0·01) at 60 minutes.

The maximum fall in the PSV was −30·6% in the MCA and −27·0% in the ACA and occurred at 32·5 and 31·5 minutes (median) respectively (table 2). The absolute changes in the PSV for each artery are shown at maximum fall and at 60 minutes from the start of infusion in figure 2. The maximum fall and fall at 60 minutes were significant (p<0·001) for both arteries.

The maximum fall in the EDV was −75·5% in the MCA and −58·1% in the ACA and occurred at 22 and 17 minutes respectively (median). This was highly significant (p<0·001) in both vessels, and remained significant in the MCA at 60 minutes (p<0·05) but not in the ACA (table 3).

The difference in the magnitude of the fall between the MCA and ACA was significant for the TAMV at maximum fall (p<0·05), and for the PSV at maximum fall (p<0·01) and at 60 minutes (p<0·05), reflecting the higher

Table 2 *Statistical analysis of the PSV*

Site	*Time*	*Mean velocity change* *cm/s*	*%*	*95% Confidence interval (cm/s)*	*p Value*
MCA	Maximum change	15·71	–30·6	12·36 to 19·05	<0·001
	60 minutes	13·85	–25·3	9·65 to 18·05	<0·001
ACA	Maximum change	9·28	–27·0	6·74 to 11·83	<0·001
	60 minutes	7·39	–21·0	4·37 to 10·41	<0·01

Table 3 *Statistical analysis of the EDV*

Site	*Time*	*Mean velocity change* *cm/s*	*%*	*95% Confidence interval (cm/s)*	*p Value*
MCA	Maximum change	3·11	–75·5	1·66 to 4·56	<0·001
	60 minutes	1·81	–44·0	0·47 to 3·16	<0·05
ACA	Maximum change	2·00	–58·1	1·02 to 2·99	<0·001
	60 minutes	0·76	–22·1	–0·04 to 1·57	NS

pretreatment velocities in the MCA. There was no significant difference in the diastolic velocity changes between the vessels. A trend was observed of a greater percentage fall in the TAMV and PSV in the MCA compared with the ACA, but this did not reach significance.

The resistance index (PSV–EDV/PSV) was calculated for both vessels. Pretreatment values were 0·93 (0·05) in the MCA and 0·91 (0·05) in the ACA. The resistance index increased significantly in both vessels to 0·97 (0·04) ($p<0\cdot01$) and 0·95 (0·05) ($p<0\cdot05$) respectively at maximum fall. At 60 minutes the resistance index was still significantly increased in the MCA 0·95 (0·04) ($p<0\cdot05$), but had returned to pretreatment levels in the ACA.

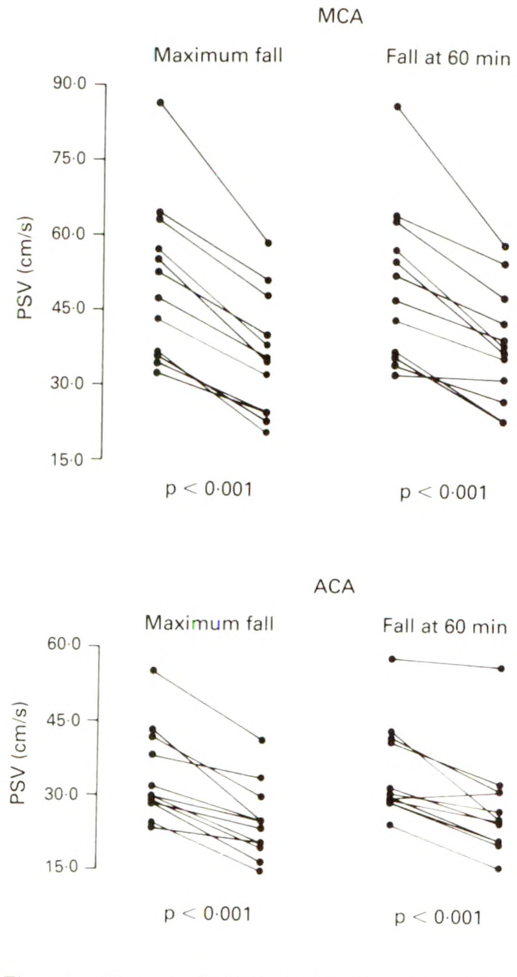

Figure 2 *Change in the PSV after indomethacin infusion.*

The coefficient of variation for the TAMV measurements of the group before indomethacin was 6·0% (2·6), and for the PSV was 4·8% (2·2), so that a change of greater than 12% and 10% respectively would be significant at the 95% confidence interval. These values did not alter significantly at maximum fall or 60 minutes. The coefficient of variation for the EDV was 21·1% (16·9), reflecting the effect of small changes on already very low diastolic velocities seen in the presence of patent ductus arteriosus.

In the six untreated infants studied serially, the coefficient of variation for the TAMV measurements throughout the 30 minutes was 7·2 (6·1)%; for the PSV measurements it was 5·4 (3·2)%; and for the EDV 15·4 (11·2)%. These are not statistically different from the pretreatment values for variability in the 11 study infants and provide evidence that there were no consistent changes induced by the study procedure.

In all infants the echocardiographic assessment at 60 minutes still showed abnormal Doppler patterns in the pulmonary artery consistent with left to right ductal shunting, with no significant change in the M mode left ventricle dimensions and left atrial to aortic ratio (pretreatment 1·57 (0·28), 60 minutes 1·56 (0·24)).

The efficacy of indomethacin in closure of the ductus did not appear to be altered by slow infusion. Ductal closure occurred in seven. One infant required surgical ligation after two courses failed to produce sustained closure of the ductus. In another infant ductal closure occurred after the second course, while two others had significant reduction in the ductal flow but without loss of the ductal murmur; on follow up one has subsequently closed and the other is awaiting surgery.

Discussion

Our study is methodologically different from previous studies in several aspects. First, duplex scanning (which employs pulsed Doppler) allows visualisation and correction for the angle between the probe and artery (if the angle is not close to zero degrees), while the continuous wave Doppler methods used in previous studies[1 4 6 7] are 'blind' and assume a constant angle between the probe and artery and constant site. This may result in errors in an intermittent study.[9] Second, we have reported the changes in all parameters, TAMV, PSV, and EDV, along with coefficient of variation data and used a larger number of velocity waveforms in their calculation.[10] Third, the ACA was insonated nearer its origin where it is of larger diameter and at a comparable site despite intermittent technique. Fourth, we have reported only first dose studies as the combination of first and repeated doses may be misleading as two studies[1 4] showed no significant fall with repeated bolus doses of indomethacin.

Finally, we have used larger numbers of infants for statistical analysis than have been used in previous studies.

Our results show that slow infusion of indomethacin was associated with a significant reduction in the cerebral blood flow velocity parameters of TAMV, PSV, and EDV at maximum change as measured by duplex scanning. The changes were sustained to 60 minutes for the TAMV and PSV in both vessels studied. The changes in TAMV at one hour (–31·6% (MCA) and –24% (ACA)) are of a similar order to those of previous reports using rapid infusion of indomethacin where falls in mean velocity of 28%[4] and 20%[7] were seen in studies using continuous wave Doppler and 38%,[2] 35%,[3] 36%[5] in those using duplex scanning. In our study the maximum fall usually occurred by 30–40 minutes for both TAMV and PSV. This differs from the abrupt fall in mean velocity measurements in the first five minutes seen after rapid administration of indomethacin,[1 6 7] which we have also seen in earlier studies in our unit.

In the MCA, the TAMV and PSV changes were greater in magnitude, tended to have a greater percentage change, and the EDV a more prolonged change, than those in the ACA. No other study has compared the response in different cerebral vessels despite documented differences in Doppler parameters between the cerebral vessels under normal conditions.[11–14] It appears from our results that the effects of indomethacin on the EDV were more pronounced on the MCA than the ACA.

Diastolic velocity is dependent on the systemic blood pressure, carbon dioxide tension, vascular resistance, intracranial pressure and, in the presence of a ductus, the degree of ductal steal.[9 13 15] In our study the echocardiographic assessment at 60 minutes, which showed persistent patent ductus arteriosus with no significant change in the M mode parameters, suggests that changes in the diastolic velocity are drug related rather than ductus related and they are in the opposite direction to that seen with a closing ductus.[13] The pattern of change to the diastolic velocity observed in this study in both vessels would be in keeping with the hypothesis that indomethacin has a direct effect on cerebral blood vessels, causing a rapid constriction and increase in vascular resistance. Whether this is mediated by prostaglandin inhibition is still unknown. The more prolonged effect on the EDV in the MCA also contributed to the continued highly significant fall in TAMV in that vessel at 60 minutes. These findings suggest that there may be regional differences in the response of preterm infants' cerebral vessels to indomethacin. Conclusions based on Doppler studies of the ACA alone could underestimate the effect on CBFV to other areas of the brain.

Our findings show that slow infusion of indomethacin causes a significant reduction in TAMV, PSV, and EDV in both the ACA and MCA. The fall in these values is more gradual than with rapid infusions. Indomethacin remains a useful and effective treatment for patent ductus arteriosus in preterm infants, but should be used with caution as we conclude that administration by slow infusion does produce haemodynamic alterations to the cerebral circulation.

Dr NC Austin was supported by The Jules Thorn Charitable Trust.

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Archives of Disease in Childhood 1992; **67**: 855–859

Randomised trial of umbilical arterial catheter position: Doppler ultrasound findings

S T Kempley, H R Gamsu

Abstract

Umbilical arterial catheters (UAC) were randomly assigned in 69 infants to a high (n=36) or to a low (n=33) position. Serial Doppler ultrasound measurements of blood flow velocity in their superior mesenteric arteries, coeliac axis, renal arteries, and anterior cerebral arteries were then obtained.

There were no differences in blood flow velocity between high and low UAC groups on days 1, 3, and 7. At 2 weeks, those infants with a high UAC still in place had significantly higher velocities in the mesenteric artery than those infants who had no catheter in place. Infants with high UACs remaining in place for more than 7 days were found to have an increase in abdominal distension and tenderness, whereas this was not the case for those with low UACs.

Catheter position has no effect on visceral blood flow if the UAC stays in place for one week or less, whereas prolonged use of a high UAC may alter intestinal blood flow and increase the incidence of abdominal symptoms.

There has been a longstanding controversy concerning the role of umbilical arterial catheters (UAC) in the aetiology of necrotising enterocolitis. Case-control studies have produced conflicting results,[1–12] with the suggestion that UACs may have an independent aetiological role in some birthweight groups while their use is merely associated with other definitive risk factors in others.[12] If it is assumed that UACs do have a truly causative role, by compromising blood flow in the mesenteric arteries, then catheters placed so that the tip lies above the origin of these arteries (high UACs) would be expected to cause more necrotising enterocolitis than catheters in a low position. However, randomised studies have failed to find any excess of necrotising enterocolitis in those infants with high catheters,[13 14] a finding confirmed in a large randomised study that we have conducted (ST Kempley, S Bennett, BG Loftus, D Cooper, HR Gamsu, unpublished observations).

This is surprising in view of the fact that catheter associated thrombosis has been found in a high proportion of infants with a UAC,[13 14] and clinical involvement of the mesenteric arteries was documented principally with high UACs. However, the majority of aortic thrombi are clinically silent and it is possible that catheters, or catheter associated thrombosis, could affect intestinal blood flow without necessarily causing necrotising enterocolitis.

We have therefore used Doppler ultrasound to document the effects of UAC position on blood flow velocity in the superior mesenteric artery (SMA), coeliac axis, and left renal artery. These major branches of the abdominal aorta originate proximally to the tip of UACs placed in a low position, but distal to the tip of UACs placed high; blood flow in them should therefore only be influenced in the latter. We have also included measurements on the anterior cerebral artery (ACA) as an index of each infant's general cardiovascular status.

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Accepted 7 January 1992

Methods

Over a two year period 147 infants admitted to our unit and requiring umbilical arterial catheterisation had their UAC randomly allocated to a high position (T6–T10) or a low position (below L3). Catheters were inserted at a median age of 2 hours to a distance determined from the shoulder-umbilicus length and the position was adjusted after a plain radiograph. The catheters were either of a plain end hole type (Argyle 3·5 French gauge (FG) or Argyle 5·0 FG, Sherwood Medical) or with a side hole and an oxygen sensing electrode at the tip (Neocath 4·0 FG or Neocath 5·0 FG, Biomedical Sensors Ltd). The initial infusate was 5% dextrose with 1 IU/ml heparin, run at 1 ml/hour in all infants. Blood pressure monitoring was performed via the UAC in all infants.

A birthweight stratified randomisation was used, with permuted blocks within strata, to help produce well matched groups. One hundred and thirty one infants had their catheter successfully inserted into the correct, randomised position. (Over this time period 36 infants had a UAC in place but were not randomised; most of these already had a UAC at the time of transfer from another hospital, or had been considered clinically unsuitable for randomisation before entering the trial.) In order to be included in the study infants were required to have a UAC placed in the position to which they had been randomised and to have had Doppler measurements within the first 24 hours of life. By excluding data from infants who had their first measurement after 24 hours we ensured that infants were not selected for study on the basis of their later clinical course, and so avoided biased groups. The final study group consisted of 69 infants, with 36 high and 33 low UACs; these infants did not differ significantly in any respect from the group who were randomised but not measured. The planned total study size had been 70 subjects, in order to give an 80% power to detect a 30% difference in blood flow velocity at a significance level of 5%.

Doppler measurements were performed at 1 day (0–24 hours), 3 days (48–96 hours), and 1 week (120–216 hours) of age, in those infants who were stable enough to tolerate scanning. Measurements were made at 2 weeks (240–316 hours) in most infants who still had a catheter in place, and in some other infants who were still in intensive care. From the original group of 69 who were all measured on day 1, 75% were measured at 3 days, 68% at 1 week, but only 29% at 2 weeks. In addition, we made serial measurements on a small number of babies whose attempted UAC placement had failed.

On each occasion we attempted to obtain measurements from the SMA, the coeliac axis, the left renal artery, and the ACA as previously described.[15] For each artery our readings consisted of a measure of blood flow velocity (the time averaged mean velocity of the peak velocity envelope, corrected for angle of insonation), and a measure of the pulsatility of the velocity waveform (the pulsatility index of Gosling and King). We chose a cerebral artery as the index artery because it would not be affected by high or low UACs, and its measurement could be combined with a clinical imaging scan performed after abdominal Doppler measurements. We found that attempting to combine abdominal Doppler with cardiac output measurements resulted in excessive disturbance to infants who were often small and needing intensive support, and so we did not consider this a suitable measurement for our study.

In our first analysis we assessed the Doppler data according to the randomised position of the UAC (regardless of whether the UAC was still in place at the time of measurement). Subsequently we looked at the influence of actual catheter position at the time of measurement (high, low, or no catheter). In this analysis the 'no catheter' group included infants whose UAC had been removed and those infants with a failed catheter placement who nevertheless were studied from day 1.

Table 1 Clinical details of the high and low catheter groups who also had Doppler measurements within the first 24 hours of life. (Quantitative measures are medians and ranges)

	High catheter (n=36)	*Low catheter (n=33)*
Birth weight (g)	1160 (540–5180)	1400 (430–3480)
Gestation (weeks)	29 (24–40)	30 (23–42)
Small for gestational age	7	7
Caesarean delivery	15	20
Apgar score:		
<7 at 1 minute	15	27*
<7 at 5 minutes	10	10
Respiratory distress syndrome	16	17
+Extreme prematurity	10	8
Interstitial emphysema	6	5
Infection	9	5
Transient tachypnoea	3	4
Aspiration	0	3
Mechanical ventilation	32	32
Highest peak inspiratory pressure (cm H_20)	20 (0–42)	22 (0–41)

Significant differences: *=$p<0\cdot01$

The data were analysed for the group of infants studied from day 1 until 2 weeks of age. They were divided into a cohort who still had a high catheter in place at 2 weeks, and a cohort who had no catheter in place at 2 weeks. We expressed the results for these two cohorts as the measurement of SMA blood flow velocity divided by ACA blood flow velocity to give the SMA:ACA ratio, in an attempt to control for general rather than specific differences in blood flow velocity between the groups.

The means and 95% confidence intervals of all the Doppler velocity measurements are presented. We had previously examined Doppler measurements obtained on the first day of life from appropriately grown infants who survived without abdominal symptoms. Velocity data from all arteries were normally distributed; for pulsatility index data only renal artery values had a skewed distribution. Unpaired Student's *t* tests were used to test the significance of differences between groups, but the Mann–Whitney U test was used to test differences in renal pulsatility index data. (There were no differences in renal artery pulsatility index between any of the groups.) A log rank analysis was used to assess differences in the duration of catheterisation, with elective removals being counted as 'curtailed follow up'.

For all randomised infants we recorded the occurrence of any abdominal symptoms (abdominal distension, abdominal tenderness or rigidity, blood in the faeces, vomiting, or large bile stained nasogastric aspirates). We divided high and low catheter groups into those who had a catheter in place for more, or less, than 7 days. The relative risk of developing abdominal symptoms after prolonged catheterisation was calculated for the high and low catheter groups (risk for >7 days divided by risk for <7 days).

Results

The high and low catheter groups were clinically well matched (table 1), the only statistically significant difference between the groups being a greater number of infants with Apgar scores at 1 minute of less than 7 in the low catheter group. The 5 minute Apgar scores were similar in the two groups, indicating that there was no difference in the incidence of clinically significant asphyxia. Similar catheters were used in the two groups (table 2), with slightly more of the high UACs being used for exchange transfusions. Positive catheter tip cultures were obtained from eight high UACs and two low UACs (just failing statistical significance, $p=0\cdot06$). High UACs were associated with less blanching or cyanosis of the lower limbs ($p<0\cdot001$), and stayed in place significantly longer than low UACs ($p<0\cdot05$).

Randomised UAC position had no effect on blood flow velocity in any of the arteries measured (fig 1). The only significant effect of UAC position was a reduction in the pulsatility

Table 2 Details of catheters used and their function

	High catheter (n=36)	*Low catheter (n=33)*
Catheter type:		
3·5 FG Argyle	4	8
5·0 FG Argyle	2	0
4·0 FG Neocath	26	22
5·0 FG Neocath	4	2
Usage:		
Exchange transfusion	5	2
Total parenteral nutrition	0	1
Duration (hours): median (range)	103 (4–614)	99 (15–709)
Emergency removal	8	10
Replacement	1	3
Positive culture from tip	8	2
Blanching or cyanosis of lower limbs	8	35*

Significant differences: *=p<0·01.
One type of low catheter not recorded.

index of the SMA with high UACs at 2 weeks of age (high: 2·22, low: 3·20, p<0·05). However, by this stage there were only four infants from the low catheter group left in the study, and only one of these had a catheter in place.

Restricting the analysis to infants who still had a catheter in place at the time of measurement yielded no significant differences between high and low catheter groups (fig 2). However, differences were seen between those infants who had a high catheter in place, and those who had no catheter (those whose catheter had been removed, plus those who had a failed insertion). For the first week of life infants with a catheter in place had lower SMA and coeliac axis blood flow velocities than those infants with no catheter. However, at 2 weeks the situation was reversed, with a significantly higher mean SMA velocity in the infants with a high UAC still in place (33 cm/s, n=6) compared with those infants who had no catheter (24·7, cm/s, n=13, p<0·05). ACA and renal artery velocity were consistently slightly higher in the group with no catheter.

Figure 3 shows the SMA:ACA blood flow velocity ratio in those cohorts defined by their UAC status at 2 weeks. A high ratio was apparent in the cohort with a high UAC in place at 2 weeks, but was not present in them at an earlier age. A similar but non-significant trend was seen in the coeliac axis. Infants who

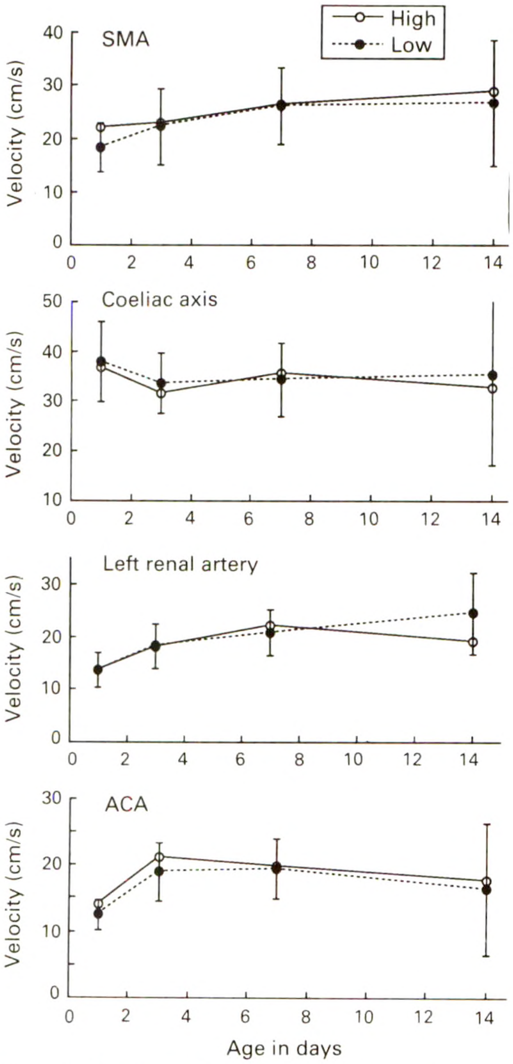

Figure 1 Randomised UAC position and blood flow velocity in the SMA, coeliac axis, left renal artery, and ACA. The mean values for high and low UACs are shown, with the 95% confidence intervals of the difference between the means as error bars on the low group values.

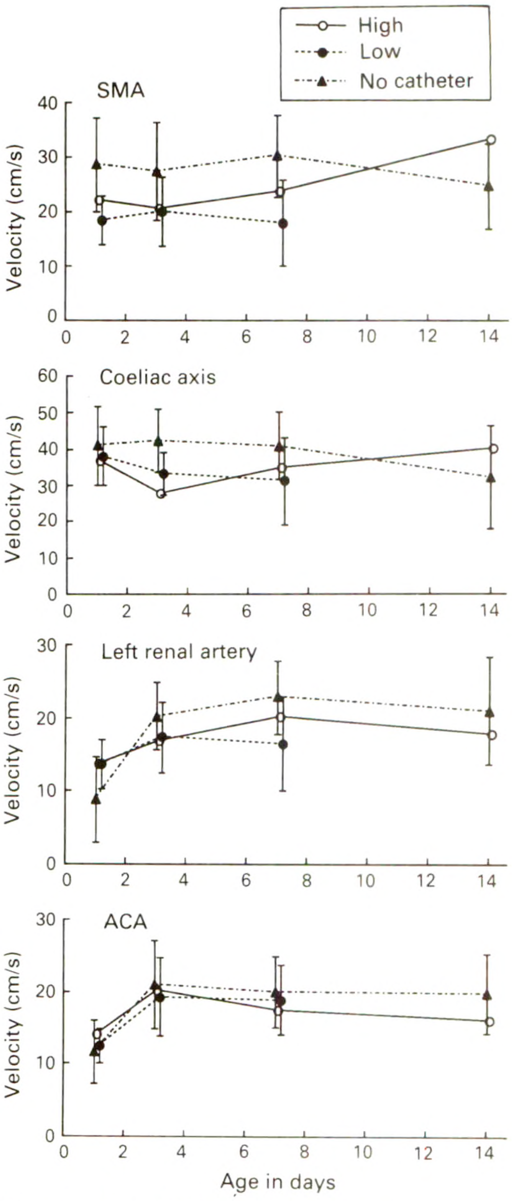

Figure 2 Actual UAC position at the time of measurement, and blood flow velocity in the SMA, coeliac axis, left renal artery, and ACA. The means for the three groups are shown. The 95% confidence intervals of the difference between the high group and the other groups are shown as error bars on the low and no catheter groups.

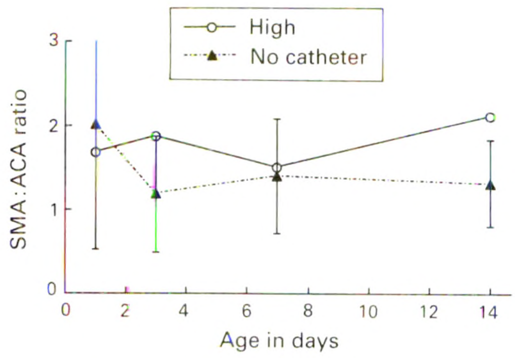

Figure 3 SMA:ACA blood flow velocity ratio. Cohorts followed up from day 1 until 2 weeks and defined by catheter status at 2 weeks. Mean values are shown with the 95% confidence intervals of the difference between the means.

had a catheter still in place at 2 weeks had a lower mean birth weight (896 g *v* 1080 g), but this difference was not statistically significant. At 2 weeks enteral feeds were being received by three of the six infants with a high UAC in place and 6/13 of those without a UAC. No infant had a clinical patent ductus arteriosus. Mechanical ventilation was still required by all of those with a UAC in place, but by only four of those with no catheter. All the catheters still in place at 2 weeks were of the Neocath type.

Using ultrasound, large aortic thrombi were clearly seen after the removal of the UAC in two infants with high Neocath catheters. One of these infants was asymptomatic, but the other died after a nearly complete occlusion of the SMA and coeliac axis. At the time symptoms developed, this infant had high blood flow velocity in the coeliac axis and the SMA.

Clinical data from all randomised infants showed that in the high catheter group there was an increased risk of abdominal distension, rigidity, and tenderness if the catheter stayed in place for more than a week (table 3). No such excess was seen in the low catheter group. There were no cases of necrotising enterocolitis among infants who had Doppler studies performed, but it did occur in three infants randomised to a high catheter and one randomised to a low catheter.

Discussion

Even though our study included an adequate number of subjects, we did not find any differences in blood flow velocity in the first week of life between those infants randomised to receive a high or a low UAC. At 2 weeks the only significant difference between the groups was an increased pulsatility index in the SMA of the high UAC group. As an isolated finding this should be viewed with some caution, as it was the only positive result from 16 tests of significance, and there was only one infant with a low UAC still in place at this stage.

Further analysis of the effects of actual catheter position does suggest that high UACs may alter mesenteric blood flow if they stay in place for 2 weeks or more. Compared with those infants who have no catheter, infants who have a high UAC in situ at 2 weeks have a raised SMA blood flow velocity, with a non-significant increase in coeliac axis blood flow velocity. This pattern is the opposite to that seen in the first week, and is not seen until 2 weeks even when we follow up the groups as cohorts. We might have expected those infants with a UAC remaining in place at 2 weeks to have lower intestinal blood flow as they were smaller, a greater number required to be ventilated, and they had a lower ACA blood flow velocity than those whose UAC had been removed. Intrauterine hypoxia,[15] patent ductus arteriosus,[16] and enteral feeding[17 18] have all been shown to alter Doppler measurements of SMA blood flow velocity, but the groups did not differ with respect to the frequency of any of these factors. We therefore believe that the abnormalities we have demonstrated are related to prolonged catheterisation rather than resulting from differences in the subject groups.

High UACs may have been expected to reduce flow in the SMA, so why should their prolonged use result in an increase of SMA blood flow velocity? Since completing this study we have seen high SMA blood flow velocity in a baby with a positive culture of *Candida albicans* from the tip of the UAC and candida emboli in the mesenteric vessels. Catheter tip infection could produce mesenteric vasodilatation as a result of local bacteraemia, and high UACs may be more prone to colonisation because they are in place for a longer period. Also, emboli or other intermittent ischaemic phenomena resulting from high UACs may have been missed by this study, and such events could eventually produce a reactive hyperaemia following multiple small ischaemic/septic episodes. We have not investigated the effects of sampling from the catheter, which may also predispose to such effects. It is important, however, to point out that high arterial blood flow velocity does not necessarily mean that there is high arterial volume flow. In the one infant with documented coeliac and SMA thrombosis, with hepatic and bowel infarction, arterial blood flow velocity remained high throughout, despite a presumably low absolute volume flow. The high observed velocity might well have resulted from a considerable reduction in vessel diameter, in much the same way that high velocity flow is seen through stenotic cardiac valves. Catheter associated thrombosis may therefore provide the best explanation of the increase of blood flow velocity in the SMA that we demonstrated.

Table 3 Numbers of infants with abdominal distension, tenderness, or rigidity according to catheter position and the duration of catheterisation. The relative risk and 95% confidence intervals (CI) of abdominal symptoms that prolonged catheterisation carries is shown for high and low catheter groups

	High catheter	*Low catheter*
Catheter in 0–7 days	8/47	7/47
Catheter in >7 days	10/22	3/15
Relative risk (95% CI)	2·7 (1·3–5·3)	1·3 (0·4–4·5)

Are our findings of any clinical significance, except in rare cases of near total mesenteric vessel occlusion? During this study we recorded all abdominal symptoms, and found an increased risk of abdominal distension, tenderness, or rigidity only in those infants who had a high UAC in place for more than one week. We are not able to comment on whether low UACs produce any Doppler abnormalities at 2 weeks, because few were still in place then. The fact that their prolonged use does not produce any increase in abdominal symptoms suggests that blood flow abnormalities did not occur. Nearly all of the catheters that were in place for more than a week were of the Neocath type, with an oxygen sensing electrode in the tip. We were therefore unable to determine whether catheter type had any influence on the incidence of Doppler abnormalities or abdominal symptoms.

We would suggest that prolonged use of high UACs may result in bowel injury without necessarily causing necrotising enterocolitis. Such bowel injury is most likely to be the result of thromboembolism. It is therefore important to differentiate thromboembolic ischaemic necrosis from necrotising enterocolitis. If we become alert to the possibility of this diagnosis in infants with high catheters, the early use of thrombolytic treatment or of surgery could improve the outcome from catheter associated thrombosis.

We would recommend that high UACs should be used initially for all infants who require umbilical catheterisation, as they remain functional for a longer period and cause less lower limb ischaemia than low UACs. Further research is needed to determine the best policy to be followed for the infant who requires catheterisation for more than a week, when high UACs may disturb visceral blood flow and cause bowel injury. It is possible that the use of less thrombogenic materials in the manufacture of catheters may reduce the incidence of thrombosis related problems, but any trials of such materials should study adequate numbers of high catheters which stay in place for more than a week, as this is the group where significant problems occur.

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Archives of Disease in Childhood 1992; 67: 860–867

SPECIAL REPORT

Screening for retinopathy of prematurity

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The demise of retinopathy of prematurity (ROP) was confidently forecast in the 1950s when supplemental oxygen was identified as a causal factor. Unfortunately this did not transpire and by the mid-1960s it became all too apparent that ROP was not solely of historical interest. The purpose of this article is to consider screening for ROP working on the basis that at present this condition is not entirely preventable, and that despite meticulous neonatal care, serious and blinding disease still occurs.[1] As in the past the ophthalmologist could neither prevent nor treat ROP, effectively all responsibilities for this condition, including its medicolegal aspects, rested with issues related to causation. The results of the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity have changed all that.[2–4] After more than 20 years of inconclusive studies, retinal ablative treatment has been shown to significantly reduce the unfavourable outcome of severe disease, both in terms of the retinal appearance and visual function.[2–4] Screening has now become a vital practical issue.

In this article the nature of the preterm population will be briefly considered, after which certain aspects of ROP will be discussed such as: its classification, incidence and severity, natural history, and treatment. Against this background the concepts, and finally, the guidelines for screening will be considered. These were drawn up by a working party convened jointly by the College of Ophthalmologists and the British Association of Perinatal Medicine.[5] Other than the guidelines themselves, the views expressed in this article are not necessarily those of the working party.

The preterm population

Over the last 40 years, survival rates for the baby born before term have dramatically increased. In 1988 the mortality rates for infants of birth weight <1500 g in England and Wales was 74%[6] and there has been a very considerable improvement in survival of the tiniest infants within this group. In the 1940s only about 8% of neonates <1000 g birth weight survived the neonatal period,[7] but in recent years this figure is in the region of 60%. Concomitant with this improved survival, the incidence of ROP has risen and it is predominantly among the most immature section of the preterm population that the advanced stages of this disease occur.

Classification

The introduction of an internationally agreed classification of ROP[8 9] (table 1) has been one of the most important events in the history of this condition. First, it has made possible direct comparison between centres, and provided the impetus for a wave of research activity. Second, if utilised fully and with an understanding of the natural history of ROP, it serves as a practical guide both to the kinetics of the ROP process and the potential for progression to severe disease. Above all, it is logical and simple to use. Being concerned

Table 1 International classification of ROP

Severity by stage

(1) *Demarcation line*
    Thin white line, lying within the plane of the retina and separating avascular from vascular retinal regions

(2) *Ridge*
    The line of stage 1 has increased in volume to extend out of the plane of the retina.
    Isolated vascular tufts may be seen posterior to the ridge at this stage

(3) *Ridge with extraretinal fibrovascular proliferation*
    This may be:
    - (i) Continuous with the posterior edge of the ridge
    - (ii) Posterior, but disconnected, from the ridge
    - (iii) Into the vitreous

(4) *Retinal detachment—subtotal*
    - (A) Extrafoveal
    - (B) Involving the fovea

(5) *Retinal detachment—total*
    Funnel:

Anterior	*Posterior*
open	open
narrow	narrow
open	narrow
narrow	open

'Plus' disease
Signs of activity which can accompany any stage and include:
Retinal vessels–tortuosity and engorgement
Iris–vascular engorgement and rigidity
Vitreous–haze

Location by zone

Retinal blood vessels grow out from the optic disc, and the zonal arrangement reflects this pattern of vascular development. Being centred on the fovea, the neural organisation of the retina is eccentric to the vascular pattern.

The zones are centred on the optic disc but zone 3 is crescentic being widest in the temporal retina and absent nasally

Zone 1
Extends from the optic disc to twice the disc-foveal distance—a radius of 30°

Zone 2
Extends from the periphery of the nasal retina (ora serrata) in a circle around the anatomical equator. In the temporal retina, in the absence of an anatomical landmark zone 3 cannot be identified precisely. Only known to be entered with certainty when the nasal retina is fully vascularised

Zone 3
Anterior to zone 2, is present temporally, inferiorly and superiorly, but not in the nasal retina

Extent of ROP

This is recorded as clock hours in each eye in the appropriate zone with the acute process, the classification of regressed ROP[9] will not be considered here.

This classification is based on three concepts, all fundamental for our understanding of the natural history of ROP, including its potential for progression. First, grading the *severity* of ROP by stage. Second, the location of the response by retinal *zone*, and third, its circumferential *extent* by clock hour on the retina. The relevance of these concepts to the natural history and routine screening of ROP will be considered later.

ROP – incidence and severity

There has been much talk of the two ROP epidemics.[1] The first, which commenced in 1942, was brought to an end about a decade later by oxygen restriction. The second epidemic began in the late 1960s, concomitant with advances in neonatal medicine, and is ongoing. Interestingly over these four decades the risk of ROP induced blindness has remained the same for infants 750–999 g birth weight (very few of whom survived in the first epidemic), but for those 1000–1500 g birth weight this risk is now very considerably reduced.[10 11] This is evidence that advances in neonatal medicine since the 1950s have reduced the risk of severe ROP in the larger infants (>1000 g), and brought to an end what could retrospectively be called the preventable epidemic. On the other hand these same advances which terminated the first epidemic have resulted in the increased survival of the very immature neonate and given rise to the second epidemic, which is currently not preventable.

Against this background it is now appropriate to consider current ROP incidence estimates. These vary[12–20] but the following figures have been published for given birth weights: <1000 g, 53·0%[12] and 88·5%[18]; ≤1250 g; 42·9%[19] and 65·8%[20]; ≤1300 g, 55·6%[15] and 75·4%[18]; and ≤1500 g, 34·9%,[13] 48·1%,[14] and 60·1%.[18] Thus incidence rises with increasing immaturity and the same can be said for severity, so that by birth weight the incidence of stage three ROP is as follows: <750 g, 37·4–40·0%; 750–1000 g, 19·0–24·7%; and 1000–1250 g, 2·7–8·5%.[18–20] A breakdown of results by gestational age is as follows: ≤27 weeks, 25·0–28·9%; and 28–31 weeks, 2·2–10·9%.[18–20] Even given an agreed classification, it is not surprising that estimates vary[12–20]; this is due to variations in survival rate, differing methods of both patient selection and the technique, and frequency of examination. The purpose of this section is not to analyse incidence rates in detail but to show the trend that the incidence and severity of ROP both rise with increasing prematurity so that below about 1300 g birth weight infants are more likely than not to develop ROP. Severe disease is confined mainly, but not entirely, to those infants of birth weight <1250 g and ≤30 weeks' postmenstrual age.*

Natural history

Appreciation of the natural history forms a logical basis for the design of a screening programme. Here three topics are pertinent: the age at onset of ROP, rate of progression, and retinal location.

(1) AGE AT ONSET

ROP only affects immature retinal vessels and does not occur therefore after the retina is fully vascularised. Instinctively perhaps one would expect the most premature and often ill neonate, with a very immature retinal vascular system, to develop ROP sooner postnatally than his/her larger more mature and relatively well counterpart. This is not so, as the postnatal age at onset is later for the more immature neonate. However, when corrected for the degree of prematurity, ROP develops over a relatively narrow postmenstrual age range.[20–22] To quote one study,[22] the onset of any ROP was between 29·7 and 45·0 weeks' postmenstrual age, with 92·1% between 30·0 and 40·0 weeks, 80·8% between 30·0 and 37·8 weeks, and 75·0% between 30·0 and 36·0 weeks. Of the 23 infants who developed ROP after term, all were relatively mature and none went on to severe (stage 3) disease. This indicates that ROP onset is linked more to the stage of development of the infant, probably at a retinal level, that neonatal events. However ROP is not present at birth, and this event is necessary for its development. The propensity for severity is governed to a large extent by the state of retinal vascularisation and of course neonatal events. Thus the later the event of birth, the later postmenstrual age at which ROP commences (albeit often shorter postnatal age). ROP commencing at a later postmenstrual age develops in a more vascularised retina and has a low risk for progression to severe disease. ROP commencing after 35 weeks postmenstrual age is most unlikely to reach stage 3. The suggestion that onset in the most immature neonate may be hastened very slightly does not substantially alter these comments.[21–23]

(2) RATE OF PROGRESSION

As with the age at onset, the rate of progression is also governed predominantly by the stage of development rather than by postnatal age, time, or severity, of neonatal events such as oxygen treatment or illnesses.[20–23] It is important to emphasise that the importance of neonatal events on the severity of ROP is not questioned, but here only the timing of ROP onset and progression are being considered. The median postmenstrual age at which the various stages develops is almost identical in two studies[20 22] and is as follows by stages: stage 1, 34·3 weeks; stage 2, 35·4 weeks; stage 3, 36·6 weeks; and for threshold ROP at 36·9 weeks' postmenstrual age (fig 1).[20]

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*Gestational age is the period in utero and is calculated as commencing from the first day of the last menstrual period. Once birth has occurred gestational age is inappropriate, and postnatal age, postmenstrual age, and postconceptional age are used. Postmenstrual age is preferred to denote gestational age plus postnatal age, in weeks. Postconceptional age is also used inaccurately and synonymously to postmenstrual age.

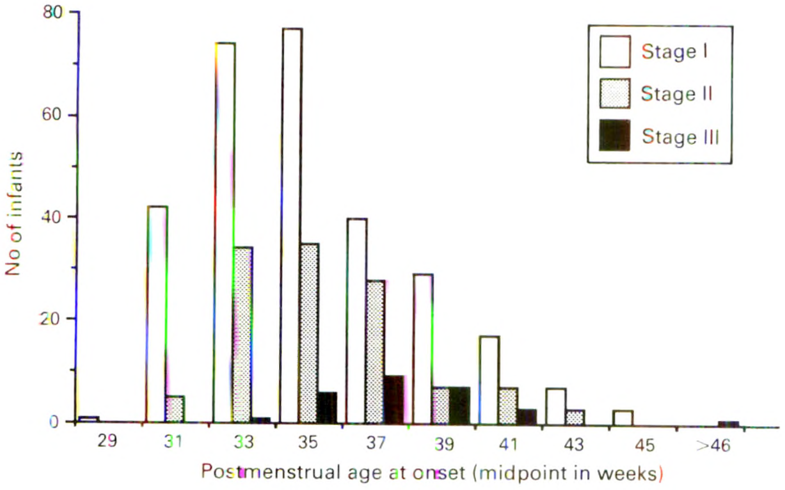

Figure 1 Postmenstrual age at development of ROP stages 1, 2, and 3 in 572 neonates.[22] *No ROP developed until the 30th week, although 201 were ≤29 weeks' gestational age. Both onset and progression on largely determined by postmenstrual age. The one infant who developed stage 3 at >46 weeks had not been examined for four weeks previously. The priority of screening is to identify infants with, or who are at risk of developing, stage 3 ROP.*

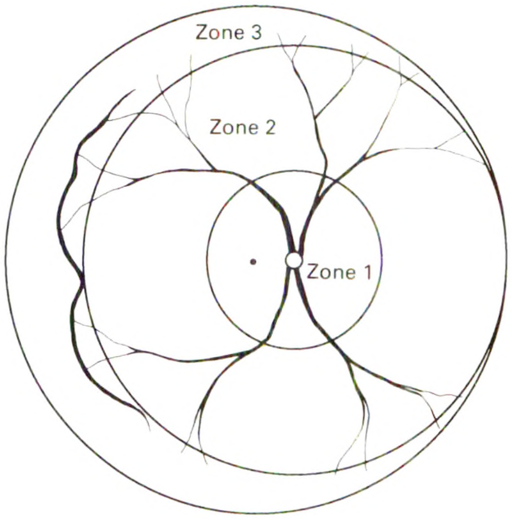

Figure 3 Stage 2 ROP confined to the temporal retina. Located in zone 3, the risk for progression to threshold disease is so low that in clinical terms it can be ignored. Central black spot denotes the macula.

(3) RETINAL LOCATION

The more premature the neonate, the less advanced retinal vascular development, the more posterior by zone the location of the retinopathy, and the greater the propensity for progression. It follows that zone 1 disease has a high tendency to progress to stage 3, but for ROP confined entirely to zone 3 this rarely if ever happens.

Traditional teaching has it that ROP commences in the temporal retina as this is the last region to vascularise. Recently it has been observed that in the most immature neonate ROP commences preferentially in the nasal retina and later extends to other regions.[22 24] Both inferior and superior retinal regions are less frequently involved at onset unless the process is located posteriorly and liable therefore to become severe. The finding of ROP in these regions early in the course of the disease is a useful indicator of the possibility of future severity (figs 2 and 3).

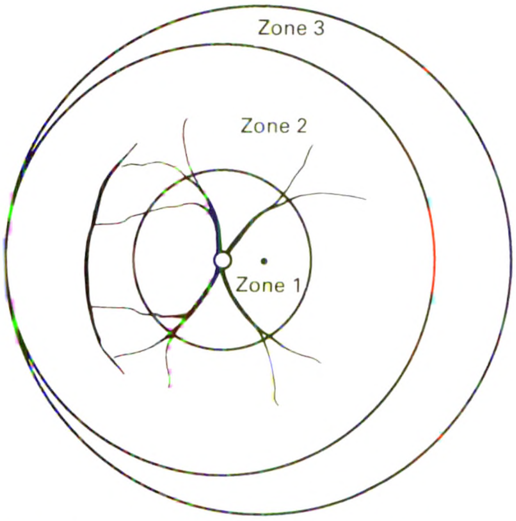

Figure 2 Stage 1 ROP in the nasal retina. This is a frequent site of initial involvement in the most immature neonate and carries a high risk for extension, by clock hour and progression to stage 2 or 3. Central black spot denotes the macula.

OTHER ASPECTS

In contrast to cicatricial ROP, which is characteristically asymmetrical, acute ROP tends to be symmetrical by stage (rarely exceeding more than one stage), although the extent of clock hour involvement can differ between the two eyes. Plus disease is a sign of activity which can be superimposed onto any stage and in practice indicates the eye likely to progress to stage 3. The most consistent signs of plus disease are dilatation and tortuosity of the posterior retinal vessels, with engorgement of the iris vessels, and vitreous haze in more severe cases.

OUTCOME OF ACUTE ROP

All highest stage 1 and 2 acute ROP undergo spontaneous resolution. Stage 3 acute ROP may, or may not resolve, depending on its severity, so that when threshold stage (table 2) is reached, full resolution is unlikely and the risk of blindness is predicted to be close to 50%.[2]

SUMMARY

Both the incidence and severity of ROP rise with increasing immaturity. Although ROP is a condition of immature retinal vessels, its onset and progression rate are determined predominantly by the stage of development rather than neonatal events. While puzzling from the point of view of basic mechanisms, this pattern simplifies screening programme design. Similarly, the location and the extent of the ROP response can also provide important predictive clues of progression or resolution.

Treatment

The treatment of ROP falls into two groups:

Table 2 Prethreshold and threshold ROP

Prethreshold ROP:
Zone 1—Any stage
Zone 2—'Plus' disease with: stage 2 or stage 3
Threshold ROP:
Stage 3—five continuous or eight cumulative clock hours with 'plus' disease

first, of the acute lesion, and second, for the late vitreoretinal complications. To take the second group first, while vitreoretinal surgery can offer surgical realignment in a proportion of cases, the visual results to date are dismal as very few attain even the lowest measurable acuity.[23]

The principle of treatment for the acute lesion is retinal ablation. A series of clinical studies started by the Japanese in the mid-1960s utilised xenon arc and laser photocoagulation, and cryotherapy to achieve this effect.[25–28] The results of these early studies were inconclusive due to problems of classification, insufficient patient numbers, and a paucity of detailed clinical data. These problems were surmounted by the introduction of the new international classification[8 9] and the mounting of a multicentre trial of cryotherapy.

MULTICENTRE TRIAL OF CRYOTHERAPY FOR RETINOPATHY OF PREMATURITY

The primary aim of this randomised study was to determine prospectively whether cryotherapy is effective in the treatment of severe acute ROP. The secondary aim was to study its natural history. Study design will not be considered.[2 3 25–28] Broadly, 9751 infants ≤1250 g birth weight without congenital anomalies were enrolled between 1 January 1986 and 30 November 1987 in 23 centres in the USA. Ophthalmic examinations commenced at six weeks postnatally and were continued at intervals of two weeks until vascularisation was complete. If prethreshold ROP (table 2) was reached the frequency of examination was increased to weekly, and at threshold (table 2 and fig 4) infants were randomly allocated to either treatment (cryotherapy) or control groups, and cryotherapy was then performed within 72 hours.

The preliminary results,[2] and those obtained at 3[3] and 12 months[4] corrected age all confirmed a significant reduction in the unfavourable outcome of threshold ROP by just under 50%, as judged by photographs and clinical examination. Indeed, because of these results the trial was terminated early due to the committee's concern for the welfare of neonates at risk who might not receive treatment. Not all threshold ROP behaved identically: symmetrical disease and that located in zone 2 had a significantly better outcome than zone 1 ROP. In addition to anatomical evidence, at 1 year treated infants had significantly better visual acuity (assessed using the acuity card procedure) than controls. However, the seriousness of ROP is highlighted, as 50·6% controls and 31·9% of treated infants fell into the low vision or blind category.[4]

SUMMARY

About two decades after first being mooted, retinal ablative treatment was found to have a significant beneficial effect on the retina, the eye as a whole, and most important on visual functions.

The cryotherapy procedure

Here only cryotherapy will be considered (reviews[27 28]), but it has recently been reported that the same effect can be achieved by laser techniques.[29 30] The introduction of portable instruments which enable laser to be delivered through an indirect ophthalmoscope hold promise for the future.

INDICATIONS

The indication for cryotherapy is threshold ROP (table 2). The term prethreshold simply alerts the clinician to the possibility of impending treatable disease threshold.

TIMING OF INTERVENTION

Once threshold ROP has been identified, delay should be kept to a minimum as the time window for treatment is short: two to three weeks at the most. ROP progression is 'locked in' to the postmenstrual age of the baby and threshold develops at a mean postmenstrual age of 37·7 weeks (range 31·9 to

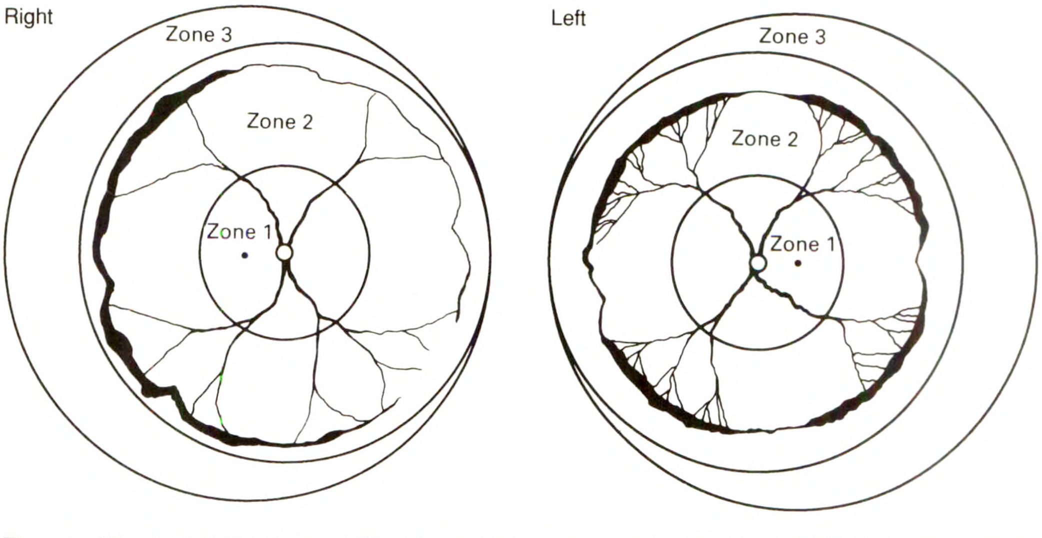

Figure 4 'Threshold' ROP in both eyes. The right eye has 5 continuous clock hours stage 3 ROP. The left eye has >8 clock hours stage 3 in total (cumulative). Note the vascular tortuosity which is not present in figs 2 and 3. This is the most frequently seen sign of 'plus' disease. If the pupil is poorly dilated, but vascular tortosity is present, the retinal periphery must be examined as this eye may be harbouring severe ROP. Central black spot denotes the macula.

50·5 weeks).[3 20] The postnatal age range is 6·6 to 23·9 weeks (mean 11·3 weeks) indicating the value of using postmenstrual age as the guide.[3 20]

THE INFANT AND FAMILY

It hardly needs to be stated that the infant requiring cryotherapy is immature and fragile. Clearly the general wellbeing of the baby must be the first consideration, but the narrow time available for treatment must not be overlooked. This is also a difficult time for parents, who perhaps are just beginning to relax about their infant's general condition. Imparting the news that their baby has a potentially blinding condition obviously requires the utmost diplomacy.

ANAESTHESIA

Cryotherapy is painful and the procedure should be performed under either general anaesthesia or local anaesthesia with sedation. More important than the type of anaesthesia is the involvement of a neonatologist or an experienced paediatric anaesthetist.

For local anaesthesia, the procedure is performed on the neonatal unit and the infant should remain in hospital overnight. Topical anaesthetics should be in eyedrop form, rather than subconjunctival and retrobulbar routes, which carry unacceptable risks.[31] Resuscitation equipment must be to hand, and an intravenous line in place for the administration of sedation or resuscitation agents before starting the procedure. Systemic complications have been reported and these include bradycardia, cyanosis, and respiratory depression,[31] but no fatalities.

CRYOAPPLICATION

After dilatation of the pupil, the cryotherapy procedure is performed under direct visualisation through the indirect ophthalmoscope (fig 5). An eyelid speculum opens the eyelids and cryotherapy is applied using a curved metallic probe of about 2–3 mm diameter that is rounded at the tip (a variety of probe designs exist). Without opening the conjunctiva (this may be necessary occasionally) the probe is placed against the globe and freezes rapidly to about −60°C. The aim of treatment is to produce a series of lesions covering the entire avascular retina, anterior to the retinopathy. The cryotherapy probe is applied to the globe until the white of the freeze is just visible ophthalmoscopically. When each application is completed the probe reheats and is moved to an adjacent area. It is important to emphasise that it is not the lesion itself that is treated but the avascular retina anterior to this. Regardless of the site of the ROP, current protocols indicate that the entire 360° globe circumference is treated and this usually requires two rows of cryotherapy.

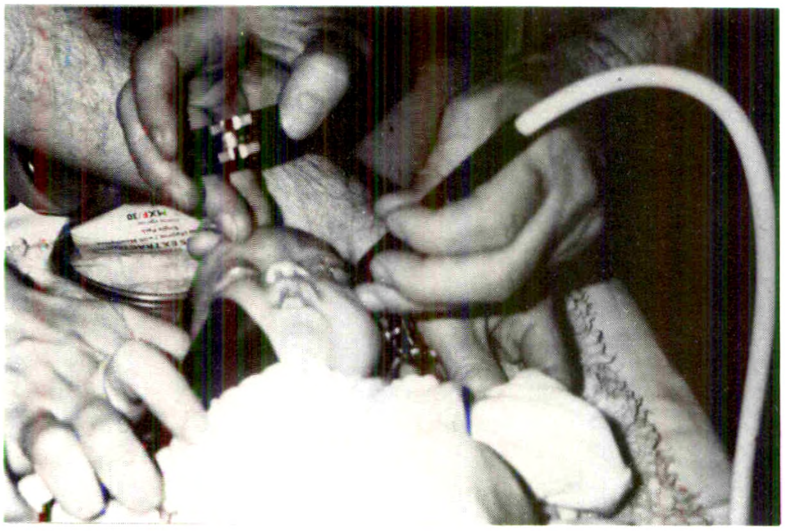

Figure 5 Cryotherapy being performed under sedation and with topical anaesthesia. The cryoprobe is placed against the sclera. Reproduced with permission from Recent Advances in Ophthalmology 8; SD Davidson, B Jay, editors. Churchill Livingstone, 1992.[28]

POSTOPERATIVE MANAGEMENT

Apart from the instillation of topical mydriatic (not atropine) for a few days, no other medication is required. Within 24–72 hours the signs of 'plus' disease begin to subside.

Retreatment may be necessary if 'plus' signs fail to subside and if it becomes apparent that certain areas of the eye have not been treated adequately: that is failure for pigmented lesions to appear in about five to seven days. Retreatment should be undertaken within two to three weeks.

COMPLICATIONS

Conjunctival lacerations and haemorrhages can occur, as can preretinal and vitreous haemorrhage.[3 28] Generally these do not cause long term adverse consequences.

Screening for ROP

The ophthalmologists' role in screening has always been less than satisfactory. In the 1960s it was suggested ROP might be prevented by the ophthalmoscopic monitoring of retinal vessel calibre,[32] but was soon found not to be feasible.[33] Furthermore, it soon became apparent that serious ROP occurred despite the most meticulous neonatal care. As ROP could be neither prevented nor effectively treated, screening was not a high priority. This all changed in 1988 when the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity reported that the unfavourable outcome in severe ROP can be significantly reduced.[2–4] Screening is now an important clinical issue and has been the subject of a number of publications.[5 34–41]

PURPOSE OF SCREENING

To identify, with the minimal use of resources: (1) severe (stage 3) ROP requiring treatment—'threshold' disease and (2) ROP with the potential to reach 'threshold'. Pertinent for infants to be transferred to another neonatal unit, or to home, before the time for stage 3 ROP.

PRINCIPLES OF SCREENING PROGRAMME DESIGN

Ophthalmic services in the UK, and presumably in many other countries, are severely stretched. Thus any screening programme should not take up an inappropriate amount of the available resources. With this in mind, and an understanding of the natural history of ROP, the time devoted to ophthalmic surveillance can be kept to a minimum. Hopefully most infants will require only one assessment.

For the remainder of this article the major issues will be highlighted utilising information discussed previously. To facilitate the reader this will be in note form.

Population at risk

Severe ROP is confined as far as can be clinically defined to infants <1500 g birth weight and ≤31 weeks' gestational age. In the UK there are about 4900 survivors (75%) of the 6600 infants of <1500 g birth weight born in the UK each year.

Timing of ophthalmic examinations

Principles: (1) onset and progression of ROP are both largely determined by postmenstrual age rather than by neonatal events, thus (2) this parameter (postmenstrual age) predetermines the time of screening examinations.

Additional points:

•The time available for treatment is narrow and the examination must be timed accordingly.

•ROP onset is rare before 30 weeks' postmenstrual age.

•A normal examination undertaken very early on (see above) may have no screening value.

•The mean age for the onset of threshold ROP is 37·7 weeks' postmenstrual age.[3 20] The earliest reported is 31·0 weeks' postmenstrual age,[20] with 5th and 95th centiles of 33·6 and 42·0 weeks' postmenstrual age respectively.

•A first examination after discharge from the neonatal unit may be too late for treatment.

•The assessment of the very sick infant may be deferred for a time, but even so, be aware of the time scale for developing serious ROP.

•Zone 1 and 2 disease should be kept under observation until resolution is well under way.

•The onset of ROP is not related to the timing of oxygen treatment or other neonatal events.

•For those without ROP, once the vessels have entered zone 3, the risk of serious stage 3 has passed and screening may cease (see below).

•For screening purposes it is not necessary to follow up all stages 1 and 2 until the point of complete resolution, it is adequate to ensure that this process is well under way.

ROP location

Principles: (1) the more posterior the location the greater the propensity for progression to severe ROP and (2) site of onset and involvement can be a useful indicator of subsequent progress—to worsen or resolve.

Additional points:

•Zone 1 and 2 ROP may progress to stage 3.

•ROP confined to zone 3 alone rarely, if ever, progresses to stage 3.

•ROP is the most immature neonate often starts in the nasal retina.

•Retinopathy involving the nasal retina (that is, zone 2 disease), and/or the vertical regions all have a greater propensity to progress to stage 3 than ROP confined to the temporal retina alone.

•The examiner can only be certain that ROP is located in zone 3 if the nasal retina is fully vascularised (see examination technique later).

Other aspects

Signs of 'plus' disease: pupillary vascular engorgement, pupil rigidity, and engorgement of the posterior pole vessels are all ominous signs—the pupil which fails to dilate to mydriatics may be the one harbouring serious ROP.

Guidelines for ROP screening

These were published by a working party convened jointly by the College of Ophthalmologists and the British Association of Perinatal Medicine (list of members at end of article).[5] A few aspects of the guidelines as originally published are expanded by the authors of this article.

WHICH BABIES

(1) <1500 g.

(2) ≤31 weeks' gestational age.

(3) No sickness criteria. The screening of larger babies who are either very ill or requiring prolonged oxygen treatment has been suggested. The working party did not consider this strictly necessary but, as such infants remain in the neonatal unit for a long time, covering the period at risk, screening of these babies would not pose a significant additional load.

The possibility of visually significant ROP developing in an infant not falling within these criteria cannot be totally excluded.

EXAMINATION PROTOCOL:

(A) Infants ≤25 weeks' gestational age.

(1) 6–7* weeks postnatally, and then (2) every two weeks until 36 weeks' postmenstrual age or until vascularisation is into zone 3.

(B) Infants 26–≤31 weeks' gestational age.

(1) 6–7* weeks postnatally, and then (2) 36 weeks' postmenstrual age, or within a week or two of this age, if to be transferred to another hospital, or to be discharged to home around this time.

For many in this group, examinations 1 and 2 will be close, or actually coincide, and one examination will suffice. It makes sense to include at least one examination before discharge from hospital. The clinician needs to understand the rationale for this protocol, and can make the following possible decisions depending on the findings at this time (34–37 weeks' postmenstrual age):

(i) No ROP, and vascularisation is well into zone 3—no review necessary for two reasons:

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*In the original publication of the working party, 7 weeks was the recommended age at the first examination Here we have taken the liberty of broadening this to 6–7 weeks.

(a) Were severe ROP to develop, by this age (postmenstrual age) the early signs of ROP would already be present and (b) stage 3 is almost never confined to zone 3.

(ii) ROP in zone 3 and regressing—no review necessary.

(iii) ROP stage 1 or 2, but it cannot be determined whether regression has commenced—review in two weeks.

(C) Babies due for transfer to another hospital or for discharge to home.

(1) Before the age of entry into the screening programme. Screening to be undertaken at the receiving hospital—staff should be alerted. If discharged to home the infant should be reviewed at the appropriate time. (2) During the screening period. Infants with ROP which has the potential to progress must be examined at the *appropriate times*. The only time available for treatment can easily be lost: simple mechanisms need to be established to facilitate review or to alert the staff at the receiving unit.

(D) Follow up

As dictated by clinical criteria on an individual basis.

The long term review of infants born prematurely, for strabismus, amblyopia, and other visual pathway defects, is beyond the scope of these recommendations, but the review of stage 3 infants is advisable as the incidence of strabismus and other problems is particularly high in this group.

WHO SHOULD EXAMINE?

Examining preterm neonates demands a high level of ophthalmic expertise and cannot be allocated to the neonatologist or the most junior ophthalmic staff.

EXAMINATION TECHNIQUE

The following are recommended:

(1) Pupil dilatation by either: (A) guttae cyclopentolate 0·5% or (B) guttae cyclopentolate 0·5% with guttae phenylephrine 2·5%. As this dilatation may last up to 26 hours weaker solutions may be employed such as cyclopentolate 0·2% in combination with phenylephrine 1·0%. All mydriatic eyedrops should be instilled at least 30 minutes before examination.

(2) Indirect ophthalmoscopy with 20 or 28 dioptre lens.

(3) The International Classification for Retinopathy of Prematurity[8 9] should be used to record clinical findings.

For the routine screening for severe disease, the use of an eyelid speculum and scleral indentor is not considered mandatory. Nevertheless, they are widely utilised[2–4 18 22 35 36] and it is recognised that these instruments do permit the evaluation of the most peripheral regions of the retina, important in determining whether the nasal retina is fully vascularised (that is differentiating zone 2 and zone 3), and accurately defining location. They also facilitate examination when the pupil dilates poorly as in 'plus' disease. Preferably, topical anaesthetic eyedrops are instilled just prior to using eyelid speculum and scleral indentor.

Conclusions

In this article we have reviewed the nature of the preterm population and have utilised the natural history of ROP as a basis for screening protocol design for this potentially blinding condition. The reader may be concerned that the criteria recommended for the neonatal period and particularly for follow up are less rigorous that is ideal. This is recognised, but ophthalmic services are stretched, and the needs of the preterm population have to be considered in this wider context. Finally, there is more to prematurity and the visual system than ROP, and hopefully as we gain more knowledge about the nature and mechanisms of these associations, these guidelines will be modified.

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SPECIAL REPORT

Report of working group of the British Association of Perinatal Medicine and Neonatal Nurses Association on categories of babies requiring neonatal care

There should be four levels of care: level 1 intensive care (maximal intensive care), level 2 intensive care (high dependency intensive care), special care, and normal care.

Definitions of neonatal care

LEVEL 1 INTENSIVE CARE (MAXIMAL INTENSIVE CARE)

Care given in an intensive care nursery which provides continuous skill supervision by qualified and specially trained nursing and medical staff. Such care includes support of the infant's parents.

LEVEL 2 INTENSIVE CARE (HIGH DEPENDENCY INTENSIVE CARE)

Care given in an intensive or special care nursery which provides continuous skilled supervision by qualified and specially trained nursing staff who may care for more babies than in level 1 intensive care. Medical supervision is not so immediate as in level 1 intensive care. Care includes support of the infant's parents.

SPECIAL CARE

Care given in a special care nursery, transitional care ward, or postnatal ward which provides care and treatment exceeding normal routine care. Some aspects of special care can be undertaken by a mother supervised by qualified nursing staff. Special nursing care includes support and education of the infant's parents.

NORMAL CARE

Care given by the mother or mother substitute with medical or neonatal nursing advice if needed.

Clinical categories of neonatal care

LEVEL 1 INTENSIVE CARE (MAXIMAL INTENSIVE CARE)

Level 1 intensive care should be provided for these babies:

(1) Receiving assisted ventilation (including intermittent positive airway pressure, intermittent mandatory ventilation, and constant positive airway pressure) and in the first 24 hours after its withdrawal.

(2) Of less than 27 weeks' gestation for the first 48 hours after birth.

(3) With birth weight of less than 1000 g for the first 48 hours after birth.

(4) Who require major emergency surgery for the preoperative period and post operatively for 48 hours.

(5) On the day of death.

(6) Being transported by a team including medical and nursing staff.

(7) Who are receiving peritoneal dialysis.

(8) Who require exchange transfusions complicated by other disease processes.

(9) With severe respiratory disease in the first 48 hours of life requiring a fractional inspiratory oxygen (Fio_2) of >0·6.

(10) With recurrent apnoea needing frequent intervention, for example over five stimulations in eight hours or resuscitation with intermittent positive pressure ventilation (IPPV) two or more times in 24 hours.

(11) With significant requirements for circulatory support, for example inotropes, three or more infusions of colloid in 24 hours, or infusions of prostaglandins.

LEVEL 2 INTENSIVE CARE (HIGH DEPENDENCY INTENSIVE CARE)

Level 2 intensive care should be provided for these babies:

(1) Requiring total parenteral nutrition.

(2) Who are having convulsions.

(3) Being transported by a trained skilled neonatal nurse alone.

(4) With arterial line or chest drain.

(5) With respiratory disease in the first 48 hours of life requiring an Fio_2 of 0·4–0·6.

(6) With recurrent apnoea requiring stimulation up to five times in an eight hour period or any resuscitation with IPPV.

(7) Who require an exchange transfusion alone.

(8) Who are more than 48 hours' postoperative and require complex nursing procedures.

(9) With tracheostomy for first two weeks.

SPECIAL CARE

Special care should be provided for these babies:

(1) Requiring continuous monitoring of respiration or heart rate or by transcutaneous transducers.

(2) Receiving additional oxygen.

(3) With tracheostomy after first two weeks.

(4) Being given intravenous glucose and electrolyte solutions.

(5) Who are being tube fed.

(6) Who have had minor surgery in the previous 24 hours.

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(7) Who require terminal care but not on the day of death.

(8) Being barrier nursed.

(9) Undergoing phototherapy.

(10) Receiving special monitoring (for example frequent glucose or bilirubin estimations).

(11) Needing constant supervision (for example babies whose mothers are drug abusers).

(12) Being treated with antibiotics.

Resources required for neonatal care

STAFFING

The British Paediatric Association (BPA) recommendation and the Neonatal Nurses Association guidelines for staffing are as follows but are subject to local conditions and are not, as yet, founded on research on dependency levels. On presentation of appropriate research findings these may require amending.

Nursing staff

Trained nurses hold registered general nurse, registered midwife, registered sick children's nurse, or the enrolled nurse certificates. Qualified nurses hold a certificate in intensive care of newborn, for example, English National Board course 405, 409, 904, 904A certificate or Joint Board of Clinical Studies certificate, that is 400, 401, 402. Maximal intensive care (level 1 intensive care) requires 5·5 nurses whole time equivalent (wte), qualified and trained per cot, high dependency intensive care (level 2 intensive care) requires 3·5 nurses (wte) qualified and trained per cot, and special care requires 1·0 nurses (wte) qualified per cot. Neonatal transport: additional provision of staff will be required by centres offering to transport sick infants.

Medical staff

Maximal intensive care (level 1 intensive care)—minimum medical staffing should consist of both an experienced paediatric registrar and senior house officer on duty and available in the intensive care area at all times with an appropriately trained consultant in charge.

High dependency intensive care (level 2 intensive care)—an experienced senior house officer on duty and available in the high dependency area at all times with a more senior member of staff on call and a consultant paediatrician in charge.

Special care—minimum medical staff for 24 hour cover: an appropriately experienced senior house officer on duty, an experienced more senior member of staff on call, and a consultant paediatrician in charge.

Neonatal transport—additional provision of staff will be required by centres offering to transport sick infants.

EQUIPMENT

The BPA recommends the following equipment and facilities:

Maximal intensive care (level 1 intensive care)

The following equipment should be available for each baby:

- Intensive care incubator, or unit with overhead hearing (1)
- Respiratory or apnoea monitor (1)
- Heart rate monitor (1)
- Intravascular blood pressure transducer or surface blood pressure recorder (1)
- Transcutaneous oxygen tension monitor, or intravascular oxygen transducer, or saturation oxygen tension monitor (1)
- Transcutaneous carbon dioxide tension monitor (1)
- Syringe pumps (2)
- Infusion pumps (2)
- Ventilator (1)
- Continuous temperature monitor (1)
- Phototherapy unit (1)
- Ambient oxygen monitor (1)
- Facilities for frequent blood gas analysis using micromethods
- Facilities for frequent biochemical analysis including glucose, bilirubin, and electrolytes by micromethods
- Facilities for necropsy by an appropriately trained paediatric pathologist
- Access to equipment for visualisation of organs such as the brain
- Access to equipment for radiological examination
- Access to transport incubator with transport ventilator

High dependency intensive care (level 2 intensive care)

Same as level 1 intensive care but without a ventilator.

Special care

The following equipment and facilities should be available for each baby who may need it:

- Incubator or cot adequate for temperature control (1)
- Ambient oxygen analyser (1)
- Apnoea alarm (1)
- Heart rate monitor (1)
- Infusion pump (1)
- Phototherapy unit (1)
- Ventilator to be used for short term ventilation (1)
- Access to frequent blood gas analysis using micromethods
- Access to biochemical analysis (including glucose, bilirubin, and electrolytes) by micromethods
- Facilities for necropsy by an appropriately trained paediatric pathologist
- Access to equipment for radiological examination
- Access to transport incubator with transport ventilator

Special care may take place on a postnatal ward, particularly in an area specially set aside for the purpose.

Units providing level 2 intensive care or special care only should have the availability of equipment for maintaining babies in optimal condition before transfer.

Archives of Disease in Childhood 1992; 67: 870–873

PERSONAL PRACTICE

Use of sedatives and muscle relaxants in newborn babies receiving mechanical ventilation

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In the 1970s sedation or paralysis was rarely considered to be necessary in the ventilatory care of premature infants. We now recognise that infants who 'fight' the ventilator may be at increased risk of a number of important neonatal complications including intracranial haemorrhage and pneumothorax. There is no consensus view on the best way of managing these infants, nor what pharmacological preparations to use in reducing the risks of these complications. When formulating an approach to inhibiting spontaneous respiration in the ventilated neonate there are three important issues to be considered. These are (i) what are the hazards of the infant breathing out of synchrony with the ventilator?, (ii) what are the effects of stress and pain associated with mechanical ventilation?, and (iii) what are the possible adverse effects of drugs used to reduce struggling or stress?

The baby and the ventilator

Anyone involved in mechanical ventilation of infants will recognise the infant who 'fights' the ventilator. Defining this is somewhat more difficult. Greenough *et al* identified infants who were actively expiring at the time of ventilator inflation as being particularly at risk of developing pneumothorax.[1] They used an intraoesophageal balloon to detect spontaneous respiratory activity and a pneumotachograph to measure tidal flow. This system is neither available nor practicable in most newborn units and other methods to recognise this pattern have been adopted. The simplest is observing the baby's respiratory activity in relation to the mechanical ventilator. Although this may successfully identify some babies, particularly those who are vigorously breathing (usually mature newborn infants) or those who are mechanically ventilated at slow rates, the observer may be in some doubt as to the interaction between baby and machine. An alternative method is to examine the beat-to-beat variability on an undamped arterial blood pressure trace. When an infant breaths out of phase with the ventilator there is increased fluctuation between the maximum and minimum systolic peaks, and if the coefficient of variation exceeds 10% we believe that this represents 'fighting'. In practice, observation alone of the blood pressure trace confirms the clinical impression of the baby showing this pattern.

Perlman *et al* showed that ventilated infants who had a fluctuating pattern of cerebral blood flow velocity (CBFV) in the anterior cerebral artery were at increased risk of subsequently developing intraventricular haemorrhage (IVH).[2] This fluctuating pattern directly reflected fluctuating arterial blood pressure as discussed above. They suggested that interventions to reduce fluctuating CBFV may reduce the incidence of IVH.

We assume that intensive care is an abnormally stressful event for newborn infants. There are many interrelated components of stress which are not understood and have not yet been unravelled.

It is likely that 'fighting' the ventilator is one factor in the stress situation. Adults who have been pharmacologically paralysed to facilitate mechanical ventilation and who become aware describe it as being a very frightening experience. This may be compounded by painful procedures undertaken on the paralysed, but aware, patient. It is not unreasonable to believe that the newborn may be similarly stressed by neuromuscular paralysis in an 'awake' state.

Muscle relaxants

Pancuronium is a steroidal non-depolarising muscle relaxant and was the first to become widely used in clinical practice. It is metabolised in the liver and the metabolites are excreted mainly in the urine. Because of the dependence of this drug on liver metabolism and renal excretion, the length of action will be prolonged in premature infants with immature renal and hepatic function. Infants and children are more sensitive to the drug than adults and take longer to clear it.[3]

CLINICAL ROLE OF PANCURONIUM

Perlman *et al* showed that muscle paralysis of babies with a fluctuating CBFV pattern led to a significant reduction in the incidence of IVH.[4] Those paralysed infants who developed IVH did so after the cessation of paralysis. In a larger randomised case control study of unselected babies, Bancalari *et al* (abstract, *Pediatric Res* 1980; **14:** A986) failed to demonstrate a protective effect of pancuronium in IVH. The infants who were paralysed actually had a significantly higher incidence of massive IVH. We have similarly failed to find a reduction in IVH in paralysed infants.

Greenough *et al* selectively paralysed infants with pancuronium who actively expired against positive pressure inspiration.[1] All the infants who were not paralysed developed a pneumothorax while only one of the 11 who were paralysed did so. The authors suggested that muscle paralysis should only be used in selected patients 'in view of the psychological problems for patients associated with use of paralysing agents'. Cooke and Rennie reviewed the incidence of pneumothorax in their unit before and after the use of muscle paralysis for ventilated newborn infants who struggled against the ventilator.[5] They showed a reduction in the incidence of pneumothorax in infants with a gestation age ≥27 weeks when pancuronium was used. Bancalari, found no reduction in the incidence of pneumothorax in a large randomised study of all ventilated newborn infants. Pollitzer *et al* similarly found no reduction in the rate of pneumothorax in an unselected group of ventilated infants who were paralysed.[6] It is not possible to agree on the clinical indication for pancuronium in the prevention of pneumothorax, but there appears to be good evidence that it does prevent pneumothorax in selected cases. Unfortunately, the criteria for this selection are difficult to apply on a regular basis in a busy neonatal unit.

Pollitzer *et al* have shown a significant reduction in the incidence of chronic lung disease in ventilated infants who were paralysed.[6] All ventilated infants with hyaline membrane disease were entered into this trial, with no selection criteria. A recent study has shown an increase in pulmonary resistance and reduction in dynamic pulmonary compliance in paralysed infants.[7] This was not a controlled study and the changes may have been due to natural progression of the disease process. None the less, there was a close temporal association between starting and discontinuing pancuronium, and deterioration and improvement in pulmonary function tests respectively. A suggested explanation for this was a loss of negative intrapleural pressure leading to impairment of drainage of lung fluid.

It may not be necessary to use any drugs to improve synchrony with the ventilator. The Cambridge group have shown that careful alterations in ventilator settings may allow the ventilator to 'capture' the infant's own respiratory efforts.[8] This in practice is time consuming and is not likely to be practical in the setting of junior medical staff making most of the ventilator adjustments in a busy neonatal unit.

POTENTIAL SIDE EFFECTS

Pancuronium causes complete loss of muscle power and ventilatory effort. If this is not anticipated, severe hypoxia may result from inadequate chest wall movement. Studies suggest that, although the acute effects of pancuronium on oxygenation are unpredictable, it does appear to reduce the variability in gas exchange over a more prolonged period.[9]

The cardiovascular effects of pancuronium are variable. Pancuronium should not alter blood pressure as ganglion blockade and histamine release are negligible. One case report suggested that pancuronium could cause severe hypotension,[10] but clinical studies of its effect on blood pressure and heart rate have shown no consistent trend.[11]

A commonly observed effect of long term pancuronium administration is that infants become oedematous. Greenough *et al* found that paralysed infants regained their birth weight sooner than non-paralysed controls despite fluid restriction.[12] A suggested mechanism was hypoperfusion of the kidneys resulting in relative oliguria. This was supported by the higher urinary osmolarity in the paralysed infants. Long term paralysis may lead to chest wall oedema and impaired compliance. The development of joint contractures has also been reported.

Drugs for sedation and analgesia

Another approach is to inhibit the baby's respiratory drive with opioid drugs. Morphine has been the most widely used in this context. Understanding the metabolism and disposition of these drugs is essential if side effects are to be avoided. These include hypotension, reduced gut motility, muscle rigidity, and fits.

Morphine is metabolised in the liver by glucuronidation and sulphation with the products being excreted in the urine.[13] Morphine-3-glucuronide (M3G) is an inactive metabolite but there is evidence that morphine-6-glucuronide (M6G) is a more potent analgesic than morphine itself and may have a more profound respiratory depressant effect.[14] It is often present in plasma in greater amounts than the parent morphine molecule. The analgesic properties of morphine may be largely dependent on the rate of conversion to M6G. Both the rate of clearance of morphine and the rate of metabolism to M6G are impaired in neonates. Therefore, higher levels of morphine are likely to accumulate but conversion to M6G will be less efficient. M6G is excreted by the kidneys and poor renal function may lead to accumulation of this metabolite in premature newborn infants. It is unclear whether these factors would result in enhanced or impaired analgesic activity of morphine in the newborn.

CLINICAL ROLE OF OPIATES

There is anecdotal evidence that the newborn infant is more sensitive to the respiratory depressant properties of morphine.[15] This may be related to impaired metabolism and/or increased penetration into the brain. There is little published data on the effectiveness of morphine in improving synchrony in ventilated neonates but our clinical impression has been that morphine, even in high doses, may not suppress the infant's ventilatory effort sufficiently to improve synchrony.

Diamorphine, which is metabolised to morphine, has recently been carefully evaluated in the newborn infant.[16] It has a rapid onset of action and is more potent than morphine. A dose regimen at the lower end of that for morphine was used because of its higher potency. A bolus dose of 50 µg/kg was followed by an infusion rate of 15 µg/kg/hour. There was a positive correlation between clearance and gestational age. Careful monitoring of blood pressure showed a small but significant fall and there was reduction in respiratory rate which was taken to indicate improved synchrony with the ventilator.

Fentanyl and alfentanil are synthetic opioid analgesics which are considerably more potent than morphine. They have the theoretical advantages of shorter duration of action and greater cardiovascular stability because of less histamine release. These advantages have made them attractive for use in the neonatal period, particularly if the shorter duration of action allows for quicker weaning from the ventilator. Marlow *et al* used a loading dose of alfentanil of 15–20 µg/kg followed by infusion of 3–5 µg/kg/hour in ventilated preterm infants.[17] These infants had reduced clearance and a prolonged elimination half life when compared with older children and adults but there was marked variability in metabolism between individuals.

ANALGESIA

The measurement of analgesic efficacy is difficult in the ventilated premature newborn. There is some evidence from pain studies in infants that the concentration of morphine required to produce analgesia is higher than in older children. The reason for this is not clear. There is no information on analgesic concentrations of morphine in premature neonates. Even if these data were available, the variation in the metabolism of morphine and the analgesic effect of its metabolites would make the accurate determination of an appropriate dosage regimen difficult.

Pain in the newborn infant may be measured using behavioural, physiological, and endocrine responses. It is difficult to assess behavioural responses in an intubated infant and physiological responses may be difficult to interpret in a sick infant. Humoral and endocrine markers may provide useful information. Anand *et al* demonstrated a marked endocrine response in infants undergoing surgery for patent ductus arteriosus who had not received adequate analgesia.[18] There was an increase in adrenaline, noradrenaline, and glucagon, with a reduction in insulin concentrations. These changes were ablated by preoperative treatment with fentanyl. There was also evidence that those who received fentanyl had fewer postoperative complications. The same workers had earlier shown a graded endocrine response depending on whether the infants where subjected to mild, moderate, or severe surgical stress.

We have recently reported a randomised study comparing the effects of morphine alone (50–100 µg/kg/hour by infusion), pancuronium alone (100 µg/kg/dose, as required), and a combination of morphine and pancuronium in reducing catecholamine concentrations in struggling ventilated neonates (abstract presented at the British Paediatric Association meeting, Warwick 1991.) Those who received morphine showed a significant reduction in noradrenaline concentrations while those who received pancuronium alone or pancuronium with morphine showed no such reduction. The reduction in noradrenaline concentrations was modest and much less than those reported in Anand's moderate and severe surgical stress groups. A number of infants were withdrawn from the morphine arm of the trial because the infants continued to struggle, probably because no loading dose was used. We concluded that infants who settle on morphine show a significant reduction in stress hormone concentrations.

Although it is not known whether intubation and ventilation are painful for premature newborn infants, behavioural clues that an infant feels pain, such as withdrawal and grimacing, are lost in paralysed infants. It may then be forgotten that procedures undertaken in paralysed but 'awake' infants are painful. This may be an additional important reason for giving continuous analgesic medication to paralysed infants.

POTENTIAL SIDE EFFECTS

Although, theoretically, opiates may prolong the length of time spent on the ventilator, we found no significant difference in the number of ventilator days between morphine and pancuronium treated infants in our randomised trial.

Hypotension is a serious potential complication of morphine. We have carefully monitored infants for this complication and found no reduction in blood pressure six hours after starting morphine by continuous infusion. Continuous blood pressure monitoring in a group of eight infants who received a bolus dose of morphine of 400 µg/kg over two hours showed no evidence of hypotension. This may be because the bolus dose was given over a prolonged period. Marlow *et al*[17] found a transient but significant reduction in blood pressure when a bolus of alfentanil was given over two minutes. The rate of drug administration is probably important.

Muscle rigidity is a reported complication of opiate administration.[19] Despite careful observation over the last few years we have only observed this effect transiently in two infants. Fits after morphine have been described in two neonates who were on standard rates of morphine infusion (32 and 40 µg/kg/hour) and the drug concentrations were not high (61 and 90 µg/l).[20] Similar concentrations have been reported without the occurrence of seizures. This may have been an idiosyncratic response and has not been subsequently reported.

Withdrawal symptoms may occur after prolonged administration of any opiate, but these are unlikely after short courses usually given to ventilated neonates. We have not recognised withdrawal symptoms in a newborn infant given morphine for therapeutic indications. A recent study has shown that withdrawal symptoms are much more common after fentanyl than morphine.[21] The symptom score was that used to assess term infants of narcotic addicted mothers. This is an entirely different group of infants on which it may not be appropriate to use the same symptom score. This may explain the high incidence of withdrawal symptoms in both groups despite careful tapering of the dose.

The endogenous opiate receptors appear to be functional in the immature nervous system and we do not know whether there may be long term effects of high concentration infusion of exogenous opiates such as morphine. The functional integrity of the endogenous opiate system must be further studied for long term effects after cessation of the infusion.

Current practice

The evidence that muscle paralysis prevents IVH is poor and its role in preventing pneumothorax is uncertain. At present we use pancuronium sparingly. The indications include mature babies (>34 weeks) who make vigorous respiratory efforts and whose ventilatory efforts are clearly detrimental to gas exchange. This decision is made clinically depending on how much the infant's respiratory effort is out of synchrony with the ventilator and the variability of the arterial blood pressure trace. Paralysis is frequently employed after thoracic surgery where an anastomosis may be torn if the infant struggles (for example, a repair of oesophageal atresia). If a paralysed infant is likely to need long term ventilation or be subjected to painful procedures, then a simultaneous morphine infusion is continued for at least four days.

We feel that infants with hyaline membrane disease who have received exogenous surfactant (Curosurf, Chiesi Pharmaceuticals, in our unit) 'fight' the ventilator to a considerably lesser extent. There is often a rapid fall in the baby's oxygen requirements after the administration of this type of surfactant, probably reflecting the change in lung compliance.

We consider that 'awake' intubation and ventilation exacerbates the infant's stress responses and therefore we start on morphine every infant who is likely to need ventilation for more than a few hours. A combination of bolus followed by infusion will ensure that an adequate plasma concentration is reached quickly and maintained. We administer the bolus dose over two hours to reduce the risk of adverse effects. From published data on volume of distribution and clearance, we have calculated a dosage regimen that aims to achieve a plasma concentration of 100 μg/l at steady state.[22] This is higher than the level shown to be analgesic in older children (65 μg/l)[23] and aims to produce respiratory depression. Because of wide interindividual variation, this figure can only be an approximation. Our present protocol is to give 100 μg/kg/hour for two hours followed by a continuous infusion of 25 μg/kg/hour. We continue the infusion until the inspired oxygen concentration is less than 40%. Because this should achieve adequate analgesic concentrations quickly, we feel that the baby is protected from repeated painful procedures such as venepuncture and heel stabs. Insertion of chest drains are, however, likely to be extremely painful and we do recommend that local anaesthetic is infiltrated superficially and into the deep tissues before insertion of the drain.

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Archives of Disease in Childhood 1992; 67: 874–878

CURRENT TOPIC

Mineral transport across the placenta

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We here review the transport of three minerals which have in common their role in bone mineralisation, their active transport across the placenta, and the rise in their placental transport rate in late gestation. The growing and differentiating human fetus is entirely dependent on its mother for the supply of nutrients and oxygen and removal of waste products. In mammals, through most of gestation this exchange process takes place across the placenta, a highly complex organ which also has other functions. Despite much research, the physiology of placental exchange and especially its control remains a poorly understood subject.

To follow the literature, it is important to have a basic understanding of the concepts and terminology involved, which in the case of calcium are shown schematically in fig 1.

By the end of normal human pregnancy the fetus acquires approximately 28 g calcium, 16 g phosphorous and 0·7 g magnesium, mostly during the third trimester (fig 2). Calcium, which is not only required for skeletal mineralisation but also acts as a regulator for a variety of intracellular functions, has attracted most attention from research workers in this field. It is, therefore, given most emphasis here.

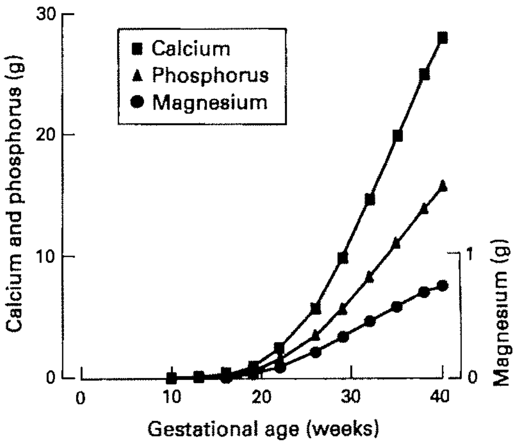

Figure 2 Total fetal content of calcium, phosphorus, and magnesium with increasing gestational age (adapted from Widdowson[1]).

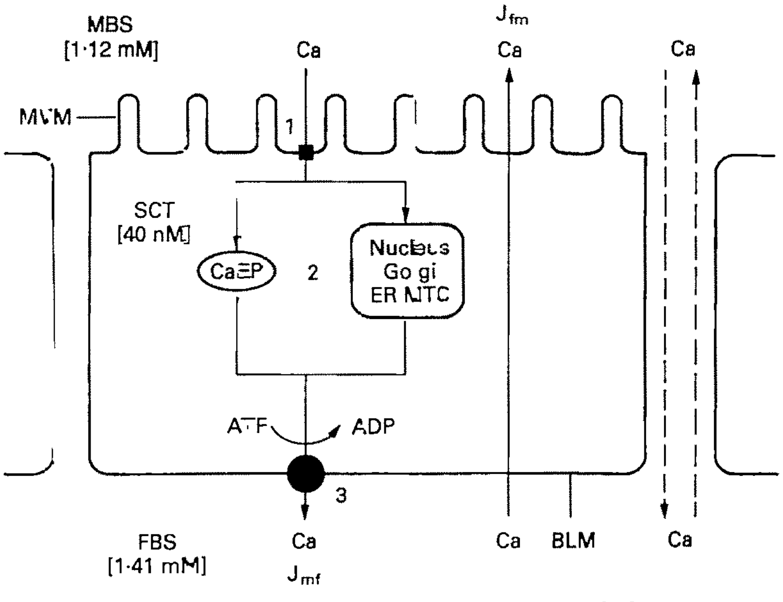

Figure 1 Schematic representation of transtrophoblastic movement of calcium. Bidirectional flux is shown with net flux across the cells. J_{net}=difference between unidirectional maternofetal flux (J_{mf}) and unidirectional fetomaternal flux (J_{fm}). Movement of calcium may also take place through hypothetical aqueous transtrophoblastic channels (which are often called paracellular channels by analogy with other barriers such as capillary endothelium but this term is not strictly correct for the placenta as the trophoblast is a syncytium), shown by the broken arrows. Approximate ionised calcium concentration is shown by [ ]; Ca, calcium; CaBP, calcium binding proteins; MBS, maternal blood space; MVM, microvillous membrane; SCT, syncytiotrophoblast; FBS, fetal blood space; BLM, basolateral membrane; ER, endoplasmic reticulum; MTC, mitochondria; ATP, adenosine triphosphate; ADP, adenosine diphosphate; ■: calcium transport protein; ●: Ca-ATPase; 1, 2, 3, see text. (Fetal capillary wall is not shown.)

Calcium

Plasma calcium exists in three forms: that which is bound to proteins, mainly albumin (40%), that which forms complexes with ions such as bicarbonate (10%), and that which is 'free' or ionised (50%); ultrafilterable calcium comprises the latter two fractions. In all mammalian species studied so far the concentration of total and ultrafilterable or ionised calcium in fetal plasma is higher than in maternal plasma[2] (table) and, therefore, because net flux occurs against a concentration gradient, active transport mechanisms are likely to be involved. Support for this comes from animal placental perfusion studies[4–6] which have demonstrated maternofetal transfer of calcium against a concentration gradient by a process which is temperature dependent[7] and is inhibited by metabolic poisons such as dinitrophenol and cyanide.[6] Calcium is transported

Human maternal and fetal concentrations of calcium magnesium, and phosphorus. Values are mean (SD) in mmol/l

	Mother	*Fetus*
Calcium	2·13 (0·15)	2·65 (0·19)
Ionised calcium	1·12 (0·06)	1·41 (0·09)
Magnesium	0·66 (0·16)	0·71 (0·16)
Phosphorus	1·43 (0·50)	1·92 (0·40)

Adapted from Schauberger and Pitkin.[3]

across the placenta faster than substances such as mannitol which are likely to cross by passive diffusion alone through the transtrophoblastic channels illustrated in fig 1.[6] This lends further support to the notion of active transcellular calcium transport.

Calcium transport across the placenta is bidirectional with marked species variation in the relative magnitudes of unidirectional maternofetal (J_{mf}) and unidirectional fetomaternal (J_{fm}) fluxes which are the determinants of net maternofetal flux (J_{net}). Thus in the sheep, placental calcium transport is reported to be highly asymmetric with a J_{mf} of 212 mg/day/kg fetal weight and a J_{fm} of 12 mg/day/kg.[8] By contrast, in the rhesus monkey, J_{mf} and J_{fm} are said to be similar (390 mg/day/kg fetal weight and 325 mg/day/kg respectively).[8]

MECHANISMS OF CALCIUM TRANSPORT

Transcellular placental calcium transport must involve at least three steps (fig 1):

(1) Influx of calcium ions from maternal plasma across the microvillous (maternal facing) trophoblastic membrane into the trophoblastic cytosol;

(2) Movement of calcium through the cytosol without causing large fluctuations in the cytosolic ionised calcium concentration;

(3) Efflux of calcium ions from cytosol across the basolateral (fetal facing) trophoblastic membrane and hence across the fetal capillary and endothelium into fetal plasma.

In other transporting epithelia the intracellular ionised calcium concentration is maintained at a low resting value of 10^{-7}M in comparison to the extracellular concentration of 10^{-3}M.[9] Recently it has been shown that trophoblast cytosolic ionised calcium concentration is $4{\cdot}2\times10^{-8}$ M.[10] It is thought that calcium enters the trophoblast as a charged ion[11] using a specific carrier in the microvillous membrane,[12 13] probably under the influence of the combined electrical and chemical ionised calcium concentration gradient across the microvillous membrane.

An efficient mechanism for cytosolic compartmentalisation and/or buffering of calcium ions in transit is likely to exist in all calcium transporting epithelia if cell viability is to be preserved. Likely candidates for this process are cytosolic organelles such as mitochondria, Golgi and endoplasmic reticulum,[11 14 15] and calcium binding proteins (CaBP). The latter have been identified in animal[16 17] and human[18] placentas. In the rat, the rapid increase in placental concentration of CaBP and its mRNA during the period of increased rate of fetal growth and calcium accumulation in late gestation suggests that this protein may be involved in placental calcium transport.[16 19] CaBP may enhance the diffusion of calcium through an aqueous compartment,[20] and it has been calculated that the presence of CaBP in enterocytes enhances cytosolic calcium diffusion by some 60 to 70-fold.[21] Thus, CaBP may act as an intracellular shuttle to facilitate the transport of calcium through trophoblastic cytosol.

It is not known how the efflux of calcium ions out of the cytosol across the basolateral membrane of the placenta occurs. One possibility is that it is translocated by a calcium and magnesium dependent adenosine triphosphatase pump (Ca-ATPase) as this has been identified in animal[22 23] and human[23 24] placental homogenates. Immunohistochemical and fractionation techniques have localised its presence to the basolateral (fetal facing) membrane of the human placenta.[23 25] Among its activators are calmodulin[25] and, in other tissues, acidic phospholipids, long chain polyunsaturated fatty acids, and phosphotidylinositol.[26]

CONTROL OF PLACENTAL CALCIUM TRANSPORT

Factors which might effect the net maternofetal transfer of calcium include maternal and fetal placental blood flows, maternal and fetal calcium concentrations, together with the activity of placental transport mechanisms and factors which regulate them. As already mentioned, fetal accumulation of calcium occurs mainly in the last third of pregnancy and, in keeping with this, maternofetal transport of calcium in the rat increases some 70-fold over the last six days of gestation.[27] This is more than can be accounted for by an increase in functioning placental surface area or in blood flow. To account for the total fetal content of calcium in a normal full term infant, it has been calculated that 170 litres of maternal plasma would have to be cleared of its plasma calcium content.[28] With an estimated uterine blood flow of 500 ml/min at term,[29] the rate of calcium delivery to the placenta by the blood stream is unlikely to be directly rate-limiting in its maternofetal transfer. However, we have found that chronic reduction of uterine blood flow in the rat does result in decreased maternofetal transfer of calcium,[30] perhaps through an indirect link such as placental ischaemia resulting in a depletion of the energy supply necessary for active placental calcium transport.

Indirect evidence suggests that the maternal plasma calcium concentration may also influence placental calcium transport. Maternal dietary deficiency leading to a maternal calcium concentration as low as 1·0 mmol/l resulted in the birth of infants with rickets whose plasma calcium concentrations were around 1·6 mmol/l.[31] Poorly treated maternal hypoparathyroidism resulting in maternal hypocalcaemia can lead to transient congenital hyperparathyroidism[32]: it is postulated that under these conditions decreased net placental calcium transfer leads to fetal hypocalcaemia and it is this which in turn leads to fetal hyperparathyroidism. Conversely, transient neonatal hypoparathyroidism has been reported in infants born to hypercalcaemic mothers due to untreated hyperparathyroidism.[33] Thus, in humans, placental calcium transport may be dependent on maternal plasma calcium concentration. In animal studies divergent results have been obtained, suggesting marked species variation. For example, in the rat, chronic maternal hypocalcaemia induced by maternal vitamin D deficiency and thyroparathyroidectomy did not alter the maternofetal calcium flux compared with sham operated animals.[34]

The placenta has no nerve supply and therefore the changing transport rate during gestation must be either an inbuilt effect of placental growth and differentiation or must result from changes in hormones (or other controlling factors) produced by the mother, fetus, or placenta itself. Calcium regulatory hormones include 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), parathyroid hormone (PTH), calcitonin, and other peptides secreted by the parathyroid glands, for example, parathyroid hormone related protein (PTHrP).

There are reports of maternal vitamin D deficiency leading to neonatal rickets,[35] suggesting that maternal vitamin D might be necessary for placental calcium transfer. The presence of cytosolic receptors for $1,25(OH)_2D_3$ in human and rat placenta[36] and of CaBP (which is a molecular marker of the action of $1,25(OH)_2D_3$ in tissues such as intestine) in human[18] and rat[16] placenta appears to support the idea. Potential fetal sources of $1,25(OH)_2D_3$, which may be important if control is from the fetal side, include that transferred from maternal plasma,[37] that synthesised from the fetal kidneys,[38] and that synthesised by the placenta itself.[39]

Direct study of the role of vitamin D on placental calcium transfer has demonstrated some species differences. In sheep, maternal treatment with 1α-hydroxycholecalciferol[40] or prolactin[41] stimulated maternofetal transfer of calcium — the latter hormone could have exerted its effect on the placenta by increasing maternal $1,25(OH)_2D_3$ concentration. Fetal nephrectomy led to a marked decrease in fetal plasma $1,25(OH)_2D_3$ concentration with reversal of the usual maternofetal calcium gradient which was restored by infusion of $1,25(OH)_2D_3$ into the fetal circulation.[42]

By contrast, in rats, maternal vitamin D deficiency did not affect total fetal calcium content,[43] and there was no effect on the maternofetal calcium gradient after fetal nephrectomy.[44] However, on the fetal side of the placenta, $1,25(OH)_2D_3$ (whether injected subcutaneously into the fetus or perfused into the fetal side of the placental circulation) also had an effect in this species in that it stimulated maternofetal calcium flux across placentas of rat fetuses which had been previously parathyroidectomised by decapitation but not across placentas of intact fetuses.[45] Because PTH is an important trophic stimulator of $1,25(OH)_2D_3$ synthesis, it is likely that the parathyroidectomised fetuses had a lower plasma $1,25(OH)_2D_3$ concentration compared with intact fetuses. This suggests that this hormone only stimulates placental calcium transfer when its plasma concentration is low to start with [45]As might be expected from the above, PTH (when injected subcutaneously into the fetus but not when perfused on the fetal side of the placental circulation) stimulated placental calcium transfer across placentas of parathyroidectomised fetuses but not across placentas of intact fetuses.[45]

In 1985 it was reported that the concentration of PTH bioactivity was higher in fetal than maternal plasma whereas the converse was true of the immunoreactivity of PTH.[46] This led to the suggestion that the fetal parathyroids may secrete a second peptide which acts functionally, but not chemically, like PTH. It was later reported that addition of fetal parathyroid gland extract to autologous fetal blood used to perfuse placentas of thyroparathyroidectomised sheep fetuses in situ led to an increase in the rate of calcium accumulation in the fetal blood reservoir.[47] Using a similar experimental model it has been shown that addition of PTHrP (isolated from a human cancer cell line) but not bovine PTH (1–84) or rat PTH (1–34) resulted in an increase in the rate of calcium accumulation in the fetal blood reservoir.[48] These authors suggested that the second peptide produced by fetal parathyroid glands may be similar to the hypercalcaemic PTH-rP implicated in the humoral hypercalcaemia of some solid tumours.[49] However, because of technical difficulties precise quantitative data are difficult to obtain, and the conclusion that this oncofetal protein may have a part to play in the regulation of calcium transport by the placenta remains to be confirmed in other preparations and species. In the rat, two human PTHrP fragments (1–34 and 75–86), when perfused into the fetal circulation of the placenta, could not be demonstrated to have an effect on the maternofetal transfer of calcium.[50]

Calcitonin may also have a part to play in that, in chronic maternal calcitonin deficiency in sheep, induced by thyroidectomy with thyroxine replacement, a significant increase in total fetal calcium content was found, whereas calcitonin replacement led to normalisation of the fetal calcium content.[51]

Phosphate

During the latter part of gestation, net maternofetal transfer of phosphate is against a concentration gradient (table). Active transport processes are therefore again likely to be involved. In kinetic studies of uptake of phosphate from the maternal or fetal circulations of perfused guinea pig placenta, uptake from the maternal circulation exceeded that from the fetal, implying a net maternofetal flux. Uptake was sodium dependent and was reduced by anoxic conditions or metabolic poisons.[52 53] In vitro studies of transport across human placental microvillous membrane has, interestingly, shown that phosphate transport is reduced by PTH[54] and is modulated by pH, temperature, and sodium and amino acid concentration.[55 56] Apart from this, little is known about the factors which regulate placental phosphate transport and indeed whether phosphate is the molecular form in which phosphorus is transported to the fetus.

Magnesium

The fetal plasma concentration of total and ultrafilterable magnesium again exceeds that of maternal plasma[57] (table), and a magnesium pump must therefore be postulated. In support of this, in the rat unidirectional maternofetal transfer of magnesium is considerably higher than that of a passive diffusional marker, is reduced by the addition of cyanide, is temperature dependent,[58] and depends on the activity of a sodium/magnesium ion exchanger.[59] Interestingly, amiloride, an inhibitor of other sodium exchangers, has been demonstrated to reduce fetal accumulation of magnesium when injected into pregnant rats.[60]

There is no direct information on the regulation of placental magnesium transport, but an insight can be gained by observing the effects of therapeutic and experimental manipulations of maternal magnesium concentration on fetal magnesium concentration and content. In humans, treatment of pre-eclampsia with intravenous magnesium sulphate led to maternal and fetal hypermagnesaemia,[61] suggesting that either the 'magnesium pump' is not normally saturated and/or increased diffusion across the placenta. Again, there are differences between species: acute maternal hypermagnesaemia in the rat led to only a slight increase in fetal plasma magnesium concentration.[62] Chronic magnesium deficiency in the rat, however, resulted in decreased fetal plasma magnesium concentration and in total fetal magnesium content.[57]

Conclusion

Placental transport of minerals and its regulation is a highly complex and largely ill understood phenomenon. Much of our knowledge remains fragmentary and there is a great deal that cannot be explained. For example, in relation to the three minerals discussed here, what are the precise placental mechanisms of transfer and are they controlled by maternal, fetal, or intrinsic placental factors or a combination of all three?; how do these factors interact with respect to maternal supply and fetal need?; and what 'switches on' the increased rate of transfer of these minerals in late gestation? These are just a few of the questions which need to be addressed before we achieve a fuller understanding of mineral transport across the placenta.

We thank Professor RDH Boyd and Dr CP Sibley for their critical review and helpful suggestions Financial support by the National Fund for Research Into Crippling Diseases, Birthright, and the North West Region Health Authority is gratefully acknowledged.

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Archives of Disease in Childhood 1992; 67: 879–881

PERSONAL VIEW

Putting the clock back 30 years: neonatal care since the 1991 NHS reforms

Catherine Pope, David Wild

The future of specialist services like neonatal intensive care seems to have been overlooked in the latest round of NHS reforms; yet the changes introduced by the NHS and Community Care Act 1990 may well have important consequences for such services. This paper examines the development of policy for the care of neonates, in particular the establishment of regional neonatal intensive care centres. It is based on informal interviews conducted with clinicians and policy makers concerned about the future of the services they are responsible for. The paper argues that current policy to devolve neonatal intensive care services is in opposition to established clinical opinion, and further, that it may actually contradict some of the stated aims of the white paper.

In line with government thinking in other areas, the NHS white paper, *Working for Patients* (1989), aimed to decentralise control of health care, and encourage competition. A central tenet of the reforms was the devolution of decision making in the NHS hierarchy – from region to district, and from individual districts to individual units. Whatever the ideological and/or political objections to this new look NHS (and there were many) there were some areas of health care provision where the new ideas could and, if the evidence so far is to be believed, did work.[1 2] Out in the districts, providers who knew what they could provide and to whom, in relatively stable areas like elective orthopaedics, found contracting services fairly straightforward. At regional level the focus shifted towards evaluation and auditing services rather than organising and directing them.

According to the white paper, supraregional specialties (such as the national heart and liver transplant programmes) would continue to require centralised funding and coordination, but, it suggested, regional and supradistrict services could be incorporated into the contracting process. The assumption that neonatal intensive care could be coordinated and funded at district level appears flawed for several reasons. The clinical evidence and literature support regional provision of neonatal intensive care. The current pattern of provision is informed by both the clinical evidence and the advice of numerous governmental committees. In addition, as this paper suggests, devolution of neonatal care may compromise patient access to services, limit specialist training, and impede the progress of medical research.

Historical precedents for regional neonatal centres

Thirty years after Dr Crosse founded the premature baby unit at Sorrento Maternity Hospital in Birmingham the Joint Subcommittee of Standing Medical Advisory Committee and Standing Maternity and Midwifery Advisory Committee (1961) recommended the creation of a comprehensive programme of care for neonates. In the same year the Report of Central Health Services Council argued that special care facilities would reduce neonatal mortality. This was formalised by the Sheldon report,[3] which advocated a two tier system of provision, with special care baby units in each district for low birthweight babies and those with illnesses unique to the newborn, and neonatal intensive care, providing higher level care at specialist teaching centres. As well as centralising expert care the latter were regarded as a prerequisite for training doctors and nurses in the special care required by the illest neonates. Though initially it was suggested that centralisation might increase the risk of infection (either as a result of deprivation of breast milk or nosocomial factors) or the possibility of over aggressive treatment, these fears proved unfounded. The consensus was that 'within each regional health authority one to three neonatal intensive care units should be established to drain the intensive module of neonatal care. Such units should be sited where the high risk obstetric service exists and where specific expertise in neonatal intensive care exists, preferably in association with an academic department of paediatrics'.[4]

Three reports of the Social Services Committee during the 1980s (1980, 1984, 1988) recommended the addition of a third tier to neonatal services such that all districts should provide short term care, backed up by subregional facilities at larger maternity units and a regional specialist perinatal centre. While the 1985 Maternity Services Advisory Committee report *Maternity Care in Action* appeared to endorse the earlier two tier system, the sub-

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sequent Royal College of Physicians report (1988) reiterated clinical support for the three tier system. By the mid to late 1980s the future of regional neonatal and perinatal centres seemed secure. There was strong research evidence that neonatal intensive care was effective in lowering mortality for low birthweight infants[5] and it seemed that policy makers and clinical practitioners were in broad agreement about the provision of such care.

Most regions had established or were working towards a three tier system for neonatal care when the NHS and Community Care Act effectively abolished the regional framework for centralised services. Following the act six of the English regional health authorities abandoned regional support for neonatal intensive care, six devolved decision making about neonatal intensive care to districts, one has managed to maintain its regional contract, and one is as yet undecided. In the words of one neonatologist, the reforms were tantamount to 'putting the clock back thirty years. Neonatal intensive care is a highly specialised service and what they are doing, I'd compare it to doing renal dialysis or transplants in a general practice. It can't be done'.

Discussing the current situation with clinicians and policy makers it is apparent that there are at least four areas in which devolution of neonatal services is problematic. First the system of financing, both in terms of setting prices and allocating funds. Second, the coordination, and crucially, monitoring and control of such services. Thirdly the place of clinical research in the new system, and fourthly, related to this the future of specialist training and education in the field of neonatology.

In terms of financing, neonatal intensive care poses some peculiar problems, not least because it is a service which involves two patients – the neonate and the mother (or mother to be) – under two separate but related forms of care (neonatal and obstetric). Conventional patient information systems, now used to calculate and record costs, were not designed to link these two costs – nor do they have any facility for including additional extras such as the added hotel costs of accommodating other relatives, like the baby's father As a result many providers are forced to operate unrealistic flat rate charges for neonatal intensive care. For those providing care, with one eye on the profit margin, such fixed prices are most favourable with average or shorter than average lengths of stay and, by implication, with the least complicated cases. Yet the primary function of intensive care is to provide for the illest, most premature babies, in need of complex and often lengthy, medical treatment Such cases are likely to be the most unpredictable in terms of costs.

Problems encountered in setting prices for such services are often eclipsed by difficulties in establishing who should be charged. In one Thames region the district of residence for neonatal admissions differs from the district of referral in over 60% of cases. Some cases may not even come from the UK: one of the London neonatal intensive care units successfully cared for quintuplets born to a non-UK resident, who had undergone infertility treatment at a private clinic in London. Nationally the expansion of NHS and private fertility treatment programmes, combined with the demographic rise in multiple births, is likely to increase the pressure on neonatal services.

Neonatal intensive care does not come cheap. It is reliant on costly equipment and highly trained staff and the support of relatively expensive services such as medical physics. A recent appraisal of equipment for neonatal intensive care in Trent[6] suggested that the financial implications of the shortfall in equipment before the reforms may have been overlooked. The ability of smaller, geographically disparate units to sustain comprehensive facilities and obtain diagnostic and clinical support therefore seems questionable.

A further worry surrounding the reforms is that they may encourage the establishment of small, less well equipped neonatal intensive care units. The new system contains few if any effective constraints or controls over those providing neonatal care, and devolution entails the loss of any central coordination and planning of facilities. Related to this there may be little incentive, or indeed financial backing, for smaller units to undertake research or to publish statistical analyses of outcome and effectiveness. Without the longitudinal research currently undertaken by academic departments linked to regional centres it may prove impossible to identify poor outcomes such as handicap or educational impairment. In addition few units will have the resources or research expertise to develop and evaluate new technology or treatment modes in what is a rapidly changing and developing field of medicine.

If smaller units become the norm and research declines this is likely to affect the quality of training for junior doctors and specialist nurses. Such units may never see or treat the full range of neonatal illnesses, and the opportunity for training staff will be missed.

The reforms and beyond

Some of the financial and organisational difficulties noted above have already become evident since the reforms. In planning terms there are difficulties for regions who have devolved services, and for those attempting to maintain centralised provision. In north east Thames, which has recently issued guidelines for neonatal services based on designated centres,[7] regional policy makers are aware that they lack formal sanctions to prevent the growth of units outside this framework. North Western Regional Health Authority, which is hoping to maintain centralised neonatal services with some 25 cots over two sites, has voiced concern that other units may 'opt out' by setting up their own neonatal care services. Staffing is also a problem. Before April 1991 North East Thames had actively attempted to respond to demand for neonatal care by funding extra cots and a new consultant post, yet the region as a whole continues to suffer from a shortfall in trained staff. Evidence suggests this is not unique to the Thames area. The staff required if most maternity hospitals were to provide neonatal care is more than double that required to provide the safe cover in a regionally planned service. As one neonatologist pointed out, 'there are not enough trained neonatologists or specialist nurses as it is, if you spread them thinly it just can't work'.

Aside from the obvious financial implications, such staffing patterns are in direct conflict with the aims of *Achieving a Balance.*[8] Specialties linked closely to neonatology, such as perinatal pathology, may also lack the necessary specialist staff. Currently there is an acute shortage of trained perinatal pathologists in the NHS and at least two English regions have no perinatal pathologists in post.

The impact of devolution is likely to be a reduction in access to neonatal intensive care; one major neonatal care centre in London continues to turn away 50% of babies referred. This is despite clinical evidence that 'the lowest feasible neonatal mortality rate in the population, however will not be achieved without ensuring that all infants who need such care receive it.'[5]

Geographical variation in access, and the quality of neonatal services persists, and is unlikely to be reduced by the 1991 reforms. Patient and physician choice may become even more limited by structural constraints and the uneven distribution of resources resulting from the devolution of services. Some areas may benefit from public and charitable pressure to maintain neonatal intensive care, but this may only provide additional intensive care cots, or fund well known units. The current campaign at St Thomas's Hospital, London for funds for a national neonatal and paediatric centre may be one of the successes – but a comprehensive, equitable neonatal service cannot be sustained in this way. In future, it seems that some components of neonatal care may become a luxury, just as they were 30 years ago.

The authors would like to thank Professor W W Holland and Ms M Morgan for their comments on an earlier draft of this paper. The Information Unit is funded by the Nuffield Provincial Hospitals Trust.

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Archives of Disease in Childhood 1992; 67: 882–884

PERINATAL LESSONS FROM THE PAST

Dr Thomas Denman of London (1733–1815): rupture of the membranes and management of the cord

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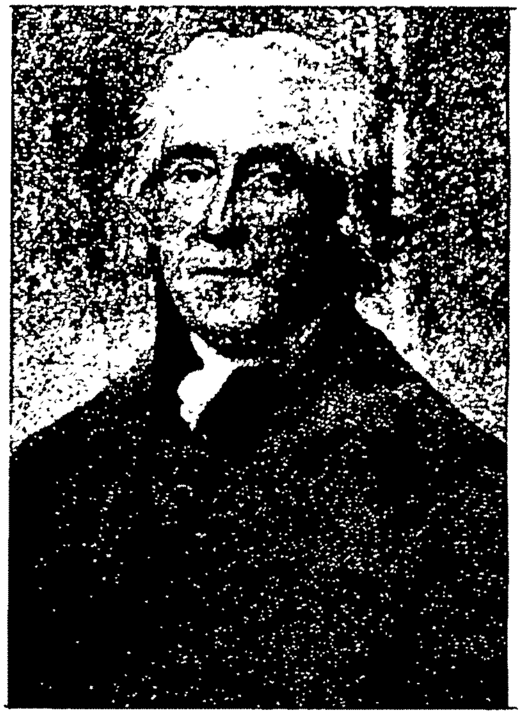
Born in 1733 Thomas Denman was the son of an apothecary in Bakewell, Derbyshire. He was educated locally and, after the death of his father in 1752, assisted his elder brother with the practice. In 1754, at the age of 21, he travelled to London to study anatomy at St George's Hospital. Within a year he ran out of money and so joined the Navy as a ship's surgeon. After eight years, with funds derived in part from the sale of French prizes captured off West Africa, he returned to St George's Hospital where he attended the lectures of Dr William Smellie. A year later, in 1764, having obtained an MD in Aberdeen, he entered practice in the City. He was also at this time appointed surgeon to the royal yacht *William & Mary* – worth £70 a year. In 1769 he was made man-midwife to the Middlesex Hospital, a post he held for the next 14 years. Also, in collaboration with Dr Osborn, he gave lectures at St George's Hospital. After Dr William Hunter's death in 1783 Thomas Denman became the leading British obstetrician and thereafter limited himself to his large consulting practice. That same year he was admitted Licentiate in Midwifery of the College of Physicians, among the first to be so admitted, and also published a successful book on *Aphorism on the Application and Use of Forceps and Vectis....*[1] An even greater success was to follow, his magnum opus *An Introduction to the Practice of Midwifery*, first published in 1794 but running through seven editions during the next 38 years. The extracts that follow in this article are taken from the third edition[2] which has been described by Dr Herbert Spencer as 'perhaps the most splendid work on midwifery in the English language whether regarded from the point of view of the format, paper, printing and illustrations of the work; the learning and knowledge that it exhibits; or the ordered, lucid, and judicial manner in which that knowledge is presented.[3]

Through his writing and teaching Denman probably wielded a greater influence upon English midwifery than that of any of his predecessors with the possible exceptions of Smellie and Hunter. He was greatly respected for his wisdom and sound judgment. His practice was conservative, for he placed great reliance on the natural process of childbirth, while not hesitating to intervene when necessary. This approach is revealed in his discussion of surgical premature rupture of the membranes which he warned against, while at the same time indicating that it might occasionally be necessary in order to induce labour either as a means of avoiding disproportion or to save the life of the fetus.



Dr Thomas Denman, 1733–1815.

On rupture of the membranes

'The premature rupture of the membranes, whether natural or artificial, has been often mentioned as the cause of much mischief, and of many tedious or difficult labours. If it be allowed, that the membranes containing the waters were intended to be the medium by which the os uteri, and other tender parts, ought to be dilated, some inconvenience must arise when these are broken and the waters discharged, the head of the child being substituted for them; and this, being a firmer and less accommodating body, cannot for a long time, be admitted within the circle of the os uteri, which will of necessity be dilated more untowardly and more painfully'.

'...it is in common observation, that far the greater number of those labours which have been considered as difficult, and which really were such towards the conclusion, were not in fact occasioned by the absolute state of the patient, but by interposition, and the desire of accelerating labours, which in their nature required a certain time for their completion. This interposition has chiefly consisted of two points of practice, both extremely reprehensible; the artificial dilation of the os uteri, and the premature rupture of the membranes. By such practice the order of the labour becomes disarranged, and there often follow occasions to exercise art, for the relief of those evils which were originally caused by the improper use of art, to the great hazard of the parent or child. So long therefore as labours proceed naturally, they may be proper objects of our observation, reason, and judgment, but cannot be considered as the objects of art. Yet when they are proved to be beyond the efforts of nature to accomplish, the assistance of art becomes justifiable because it is necessary, and we may be reconciled to the fate of the child, if the life of the mother cannot possibly be preserved by any means consistent with its safety'.

'There is another situation in which I have proposed, and tried with success, the method of bringing on premature labour. Some women, who readily conceive, proceed regularly in their pregnancy till they approach the full period, when, without any apparently adequate cause, they have been repeatedly seized with rigor, and the child has instantly died, though it may not have been expelled for some weeks afterwards. In two cases of this kind I have proposed to bring on premature labour, when I was certain the child was living, and have succeeded in preserving the children without hazard to the mothers'.

Denman's book is rich in observations and comments that are still of interest and reference today. The second subject chosen for inclusion in this short article is on:

Management of the umbilical cord

'There is yet in all things a perfectly right as well as a wrong method; and, though the advantage or disadvantage of either may be overlooked, the propriety and advantage of the right method must be evidently proved by individual cases, and of course by the general result of practice. In this, as well as in many other points, we have been too fond of interfering with art, and have consigned too little to nature, as if the human race had been destined to wretchedness and disaster, from the moment of birth, beyond the allotment of other creatures.

Perhaps the changes which take place in the body of the child, immediately after its birth, at least the manner in which they are produced, are not perfectly understood at this time. But we know if the child is in a healthy state, that it usually cries lustily and continually, when the air rushes into its lungs, which are thereby expanded. This cry, which does not seem to be occasioned by pain but surprise, is in its consequences extremely important, as it is the cause of an exertion of all the powers of the child, and enables it to acquire a new manner of living, inconsistent with, and very different from, that which is possessed before it was born. But the change from uterine life, as it may be called, to breathing life, is not instantaneous, but gradual; and the uterine life continues till the breathing life is perfected, as is proved by the continuance of the circulation between the child and placenta for some time after it has cried. As the breathing life becomes perfected, the uterine life gradually declines, and the manner of its declention may be proved by attending to the pulsation of the navel-string, which first ceases at the part nearest the placenta, and then, by slow degrees, nearer and nearer to the child, till at length it entirely ceases; so that the whole of the circulating blood ultimately resides in the body of the child, and the navel-string becomes quite flaccid. It seems reasonable to believe, that the continuance of the uterine life after the birth of the child was designed for its preservation from the accidents of its state at that time, should the acquisition of its breathing life be by any cause retarded or hindered. If then the practice of tying or dividing the navel-string the instant the child is born be followed, though it were before vigorous, it will in some cases immediately decline, and, never acquiring its perfect breathing life, may in a short time die: or, if the child were in a feeble or a dubious state, possessing only that life which it had during its residence in the uterus, as by tying and dividing the navel-string that life is destroyed before the breathing life is acquired, it must inevitably perish. We may therefore safely conclude, that the navel-string of a new-born infant ought never to be tied or divided, till the circulation in it has ceased spontaneously, nor would the child suffer, though the funis was never tied, if it was not divided.

With respect to the manner of tying the navel-string there has also been much difference of opinion, whether there should be one or two ligatures, and in what part these should be fixed. Two ligatures were advised on the presumption, that by the end of the funis next the placenta the maternal blood might be discharged, and the parent brought into great danger, as if there were two currents of blood circulating in the vessels; and by some it was also supposed proper to use two ligatures, for the purpose of retaining the blood, presuming that the placenta would be cast off more commodiously, in the manner of a gorged leech. On the contrary, one ligature has been recommended, that we might have an opportunity of draining away as much blood as possible from the placenta, by the divided end of the funis, which was supposed to produce an advantage equal to the diminution of the bulk of the placenta, and to favour its expulsion. But, if the custom of deferring to make the ligatures till the circulation in the funis ceases be established, all this reasoning in favour of one or two ligatures will fall to the ground.

Yet, as there is a possibility in the case of twins, with a single placenta, of the child yet unborn losing its blood by the divided funis of that which is born, and from the habit of using them, on the whole, I prefer two ligatures, more especially as no harm can arise from them, even if one should be useless'.

Denman was a strongly made man of moderate height and with a fresh vigorous complexion, bright blue eyes, and white hair. In character he is described as cheerful and amiable, unassuming and modest, hardworking, deeply religious and an attentive benefactor to the poor. In 1770 he had married Elizabeth Brodie at the age of 37. There were three children: a son who eventually became Baron Denman as Lord Chief Justice, and twin daughters, one of whom married a distinguished physician, Dr Matthew Baillie, and the other an equally distinguished obstetrician, Sir Richard Croft, who became Denman's associate in practice. Indeed it was with Croft that Denman planned an institution for the reception of the infants of women who were engaged as wet-nurses, for he knew how often such infants were neglected with fatal outcome.[4]

In 1815 Denman died at the age of 82 and was buried in St James's Church, Piccadilly. Let his injunction to his colleagues in 1880 be his epitaph:

'It must, however, be acknowledged that all the errors of practice do not proceed from ignorance of the art. Some of them may justly be imputed to our entertaining too high an opinion of the art, or too much confidence in our own dexterity, or too little dependence on the natural efforts and resources of the constitution'.

1 Denman T *Aphorisms on the application and use of the forceps and vectis in preternatural labours, or labours attended with haemorrhage or convulsions*. London, 1783

2 Denman T *An introduction to the practice of midwifery*. 3rd Ed. London. J Johnson, 1801

3 Spencer HR *The history of British midwifery from 1650 to 1800*. London: John Bale, Sons and Danielsson, 1927.

4 Still GF. *The history of paediatrics*. Oxford: Oxford University Press, 1931

Archives of Disease in Childhood 1992, 67: 885–886

LETTERS TO THE EDITOR

Aerosol drug delivery to intubated neonates

SIR,—We were pleased to read the two articles concerning aerosol drug delivery to intubated neonates by O'Callaghan *et al*[1] and Grigg *et al* [2] In particular, methods to determine the dosage available from the various devices should prove useful for investigators developing new means for aerosol delivery to intubated patients. We have previously described a device similar to the Aerochamber and not unlike the 'collapsible spacer' of O'Callaghan *et al.* We characterised its performance using beclomethasone dipropionate.[3] As noted in both of the new reports,[1 2] most of the drug released from the metered dose inhaler (MDI) does not reach the lung. We found just over 50% of the drug was actually aerosolised into the spacer.

With our device, the output from the tip of the endotracheal tube was 2·95±0·75% of the MDI dose, similar to that delivered by the collapsible spacer device of O'Callaghan *et al.* We also noted that this output would translate to a rather high dose/kg compared with adults. We would like to point out that if a spacer like the Aerochamber is shortened, however, then the dosage delivered from the endotracheal tube can be decreased When the length of the spacer on our device was reduced from 16 cm to 7·5 cm, the output dropped from 1·17±0·29 μg to 0·79±0·19 μg We are currently evaluating the effect of different spacer and endotracheal tube sizes on drug output. We too believe that drugs like beclomethasone, when delivered directly to the lungs, offer great promise. To that end we have begun a randomised, blinded trial of aerosolised beclomethasone versus systemic dexamethasone for the prevention of bronchopulmonary dysplasia.

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1 O'Callaghan C, Hardy J, Stammers J, Stephenson TJ, Hull D. Evaluation of techniques for delivery of steroids to lungs of neonates using a rabbit model. *Arch Dis Child* 1992;67:20–4
2 Grigg J, Arnon S, Jones T, Clarke A, Silverman M Delivery of therapeutic aerosols to intubated babies *Arch Dis Child* 1992,67: 25–30
3 Rozycki H, Byron PR, Dailey K, Gutcher GR Evaluation of a system for the delivery of inhaled beclomethasone dipropionate to intubated neonates *Dev Pharmacol Ther* 1991, 16:65–70.

Respiratory support using patient triggered ventilation in the neonatal period

SIR,—Greenough and Milner in their review of patient triggered ventilation in neonates make a serious error in the their description of the use of abdominal expansion as a trigger [1] They advocate taping the sensor capsule of the respiration detector on to the abdominal wall just below the xiphisternum, which happens to be the worst possible place for it. During inspiration, the costal margin may be pulled in by the contraction of the diaphragm to such an extent as to reduce or even reverse the movement of the abdominal wall, so that the pneumatic signal from the capsule is reduced or even abolished. The capsule should be placed, after careful observation of the respiratory movements, at the position where abdominal expansion is maximal, usually in the lower abdomen. The use of this defective technique may account for the absurdly high delays and poor sensitivity observed by Hird and Greenough.[2]

Although this is a serious point and emphasises the importance of close attention to detail, it will soon become only of academic interest. With modern techniques and attention to phase angle,[3] airways pressure triggering is now easily possible with any intermittent positive pressure ventilator, and will supersede all other techniques. Although a prospective clinical trial would seem desirable, it would be very difficult to carry out, and there is a good case for taking patient triggered ventilation as the null hypothesis and requiring those who advocate other methods to prove their superiority.

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1 Greenough A, Milner AD Respiratory support using patient-triggered ventilation in the neonatal period *Arch Dis Child* 1992;67:69–71
2 Hird MF, Greenough A Comparison of triggering systems for neonatal patient triggered ventilation. *Arch Dis Child* 1991,66:426–8.
3 Wright BM, Baker JA, Rosenthal M Airways-pressure triggered (APT) ventilation in the newborn *J Physiol* 1990,426:6P.

Professor Milner and Dr Greenough comment

We are grateful for Dr Wright's comments in response to our paper. We agree that there are considerable problems associated with the placing of the capsule, and that even when attached to the lower abdominal wall it is possible to achieve a situation in which the ventilator is then triggered by the baby's expiratory rather than inspiratory efforts. We are less optimistic that improvements in airway trigger design will overcome all problems as our experience has shown that in the first 24 hours of life, and in those of less than 28 weeks' gestation, respiratory efforts are often too erratic and insufficiently sustained for this technique

Although we consider that the place of triggered ventilation is probably secure, we remain convinced that all new techniques introduced into neonatal intensive care must be subject to carefully designed prospective control trials to assess their effects on longterm outcome.

Catabolic effect of dexamethasone in the preterm baby

SIR,—In the recent article by Brownlee *et al* their assessment of the catabolic effect of dexamethasone in the preterm infant promoted some active discussion.[1] One of the points of debate is whether the increase in blood urea observed was due solely to the effect of occult gastrointestinal haemorrhage that is seen and recognised in steroid treatment [2–4] The already falling creatinine concentrations would then be in keeping with these findings.

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1 Brownlee KG, Ng PC, Henderson MJ, Green JH, Smith M, Dear PRF. Catabolic effect of dexamethasone in the preterm baby *Arch Dis Child* 1992,67:1–4.
2 Cummings JJ, D'Eugenio DB, Gross SJ A controlled trial of dexamethasone in preterm infants at high risk of bronchopulmonary dysplasia. *N Engl J Med* 1989,320:1505–10.
3 Alkalay AL, Pomerance JJ, Puri AR, *et al* Hypothalamic pituitary—adrenal axis function in very low birth weight infants treated with dexamethasone. *Pediatrics* 1990,86:204–10.
4 Chhattriualla Y, Colon AR, Scalon JW. The use of cimetidine in the newborn *Pediatrics* 1980, 65:301–2

Premature labour

SIR,—We read with interest the recent review by Steer concerning premature labour [1] With regard to the diagnosis of premature labour, he recommends a cervical assessment in all cases and states that in patients with preterm premature rupture of the membranes (PPROM) there is no evidence that up to three digital vaginal examinations have any effect on provoking labour. However, we have found a significant negative correlation between the number of digital examinations performed and the duration of the latent period in patients with PPROM (unpublished data). This observation is supported by several previous studies.[2–4] It has been suggested that digital manipulation when assessing cervical conditions may evoke the release of prostaglandins or cause a subclinical infection that might in turn initiate the release of prostaglandins.[3] When a patient with PPROM is not in labour and there are no other indications for immediate delivery, virtually all information necessary to manage the patient can be obtained from a single sterile speculum evaluation. The common practice of performing a digital examination in patients with PPROM who are not in labour seems to shorten the interval between examination and delivery[2–4] and may expose the patient to increased risk of infection.[4]

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1 Steer PJ Premature labour *Arch Dis Child* 1991,66:1167–70
2 Schutte MF, Treffers PE, Kloosterman GJ, Soepatmi S Management of premature rupture of membranes: the risk of vaginal examination to the infant. *Am J Obstet Gynecol* 1983,395:395–400
3 Adoni A, Ben Chetrit A, Zacut D, Palti Z, Hurwitz A Prolongation of the latent period in patients with premature rupture of the membranes by avoiding digital examination *Int J Gynaecol Obstet* 1990,32:19–21
4 Lewis DF, Major CA, Towers CV, Harding JA, Arsat T, Garite TJ. Effects of digital vaginal exams on latency period in preterm premature rupture of membranes *Am J Obstet Gynecol* 1991;164:381

Professor Steer comments:

I am grateful for the comments by Drs Seidman and Mashiach. However they seem to have misread my review because they claim that I stated that up to three digital vaginal examinations have no effect on provoking labour. In fact I suggested that 'careful cervical assessment should be made on all women' and that 'up to three (examinations) when they (the membranes) are ruptured'. Nowhere do I state that the examination should be digital, and I agree with Drs Seidman and Mashiach that 'virtually all the information necessary can be obtained from a sterile speculum examination'. I also agree that this need only be performed once if a decision is made for conservative management. However, if subsequently there are signs of active labour supervening, then usually the only way of establishing whether this is really the case is to repeat the examination. Usually a speculum examination is sufficient, but very occasionally if the mother is uncooperative a digital examination may be necessary as a last resort.

In relation to the risk of digital examination, I am grateful for the references supplied; it should be noted however that of the four sources given, two appeared after I prepared my manuscript and a third remains unpublished.

Rh haemolytic hepatitis

SIR,—In his recent article on Rh haemolytic disease Professor Whittle states that extramedullary erythropoiesis secondary to fetal anaemia may obtund other liver activities, leading to reduced albumin production and hydrops fetalis.[1] However, clinical, biochemical, and histological studies made in Birmingham,[2] Bristol,[3] and San Francisco[4] between 1960–7 showed this not to be so. Indeed, some hydropic infants that I studied at necropsy had no hepatic erythropoiesis. Instead, the explanation for the liver failure was in widespread liver cell damage to be found in 10–20% of the most severely affected Rh infants. Characteristically, such infants demonstrated obstructive jaundice, marked hepatosplenomegaly, and cord blood haemoglobin concentrations below 100 g/l. Half the infants, with a mean total cord serum protein concentration of 31 g/l and a mean serum albumin of 16 g/l, exhibited hydrops fetalis. Prenatal growth retardation, haemorrhagic disease of the newborn, and neonatal hypoglycaemia were common complications, probably also secondary to the liver damage.

During this eight year period I observed only three Rh infants with signs of kernicterus. All had exhibited cholestasis. None had had 'dangerous' concentrations of serum unconjugated bilirubin. It seems likely in retrospect that these infants had had low serum albumin binding capacities.

Microscopically, the liver architecture was grossly disorganised and the hepatic cells, often multinucleated, were loaded with haemosiderin. Reticulum and collagen fibres were markedly increased, even occasionally to the point of early cirrhosis.

My studies led me to speculate that the liver damage, which I termed 'Rh haemolytic hepatitis' was due to the sequestration and sludging of agglutinated red cells in the hepatic sinusoids leading to secondary hepatic hypoxia and also to haemosiderosis. I further suggested that this was only likely to occur to any significant extent after haemolytic 'overload' had led to a splenic failure to deal adequately with the damaged circulating red cells. I still think this is likely to be the correct explanation.

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1 Whittle MJ. Rhesus haemolytic disease. *Arch Dis Child* 1992;67:65–68
2 Dunn PM. Obstructive jaundice and haemolytic disease of the newborn. *Arch Dis Child* 1963, 38:54–61
3 Dunn PM. Obstructive jaundice, liver damage and Rh haemolytic disease of the newborn. *Bulletin of the Jewish Hospital (New York)* 1965,10:92–124.

4 (A) Dunn PM. Cholestasis and erythroblastosis fetalis. Paper presented to University of California School of Medicine, San Francisco, 29 June 1967. Manuscript unpublished but available on request.
(B) Dunn PM. The significance of liver damage in severe erythroblastosis fetalis. Paper presented to the Neonatal Society, London, 2 November 1967. Manuscript unpublished but available on request.

Professor Whittle comments:

Professor Dunn seems to suggest that extramedullary erythropoeisis in the liver is unlikely to be the cause of impaired liver function in the baby affected by severe Rh disease and suggests a condition of Rh hepatitis as an alternative. Indeed he states that some of the cases of hydrops that he described showed no evidence of hepatic erythropoeisis, a most surprising observation. The references he uses are all his own, but Wigglesworth and, I suspect, most pathologists seem to have less doubt that the liver and spleen are largely replaced by erythropoietic activity in severe Rh disease.[1] Nevertheless it may well be true that such activity and the general tissue hypoxia which exists in the very anaemic baby may produce hepatic damage, but probably as a very late stage event. Hydrops, on the other hand, will usually appear once the fetal packed cell volume has fallen to about 0·15 and some time before eventual death. It should be further noted that whereas the changes described by Professor Dunn would be likely to be irreversible, hydrops will resolve once the baby has received appropriate transfusions and presumably hepatic erythropoeisis has become suppressed and normal activity recommenced.

1 Wigglesworth JS. The liver and biology system. *Perinatal pathology*. Philadelphia: W B Saunders, 1984:317

Low dose intraventricular fibrinolytic treatment to prevent posthaemorrhagic hydrocephalus

SIR,—The report of Whitelaw *et al* on the use of intraventricular streptokinase is of interest.[1] However, I am not convinced that their very good clinical outcomes were due to fibrinolytic enhancement. Streptokinase acts by combining with plasminogen with the resultant streptokinase-plasminogen complex being the plasminogen activator. It is well established that human newborns have moderate to severe hypoplasminogenaemia. This limits the amount of plasmin that could be generated. Also, the in vitro fibrin plate method that the authors used employed human fibrinogen. This reagent contains plasminogen unless the laboratory specifies plasminogen-free fibrinogen. Thus, the zones of lysis that the authors noted could be due to streptokinase in the cerebrospinal fluid combining with plasminogen in the fibrin plate and not being indicative of true fibrinolytic activity in the cerebrospinal fluid.

The authors should clarify if the human fibrinogen reagent contained plasminogen or not, and, if it did what other evidence do they have that indeed they induced a lytic condition.

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1 Whitelaw A, Rivers RPA, Creighton L, Gaffney P. Low dose intraventricular fibrinolytic treatment to prevent posthaemorrhagic hydrocephalus. *Arch Dis Child* 1992;67:12–4

Dr Whitelaw and coauthors comment:

We appreciate Professor Corrigan's interest in our paper. He questions whether we have evidence of a fibrinolytic state in the cerebrospinal fluid (CSF) during intraventricular streptokinase treatment. He is quite right in pointing out that laboratory grade fibrinogen contains small amounts of plasminogen and therefore streptokinase could have produced lysis on the fibrin plate without there necessarily being plasminogen already present in the CSF. However, we have been able to demonstrate the presence of plasminogen in CSF after intraventricular haemorrhage using an immunodiffusion method and this will be published in a future paper. The plasminogen then becomes undetectable in CSF during streptokinase treatment because it becomes incorporated in the active streptokinase-plasminogen complex. Further evidence of plasminogen activation is provided by the finding of high concentrations of fibrin degradation products in the CSF after intraventricular haemorrhage,[1] and a pilot study we have done also shows that the concentrations of fibrin degradation products rise during intraventricular streptokinase treatment. It is significant that the CSF taken before streptokinase treatment produced lysis on the fibrin plate. Finally, the intraventricular bleeding occurring during streptokinase infusion in one baby is consistent with a fibrinolytic state within the cerebral ventricle.

Thus we are accumulating evidence (which will be published in full) that there is considerable endogenous fibrinolysis in the CSF following intraventricular haemorrhage and that it is possible to augment this fibrinolysis by intraventricular streptokinase.

1 Whitelaw A, Creighton L, Gaffney P. Fibrinolytic activity in cerebrospinal fluid after intraventricular haemorrhage. *Arch Dis Child* 1991;66: 808–9.

BOOK REVIEWS

Neonatal Emergencies—Early Detection and Management. 2nd Ed. Edited by John A Black and Michael F Whitfield. (Pp 385; £50 hardback.) Butterworth-Heineman Ltd, 1991. ISBN 0-7506-1313-0.

When it first came out 20 years ago, Black's *Neonatal Emergencies* was a companion volume to his book on paediatric emergencies and was virtually one of a kind; essential reading for a budding neonatal paediatrician. The second edition has been a long time coming and, as the authors point out, during this time the care of the newborn has changed out of all recognition. There has also been a proliferation in the competition with at least four similar books on the shelves; some already into their second or third editions after only five or six years. Although the authors have added a lot of new material, the age of the original still shows through

Neonatal Emergencies is really a textbook of acute neonatal paediatrics. Starting with the background to fetal and neonatal disease, it goes on to cover the usual topics of resuscitation, birth injury, the management of the very low birthweight infant in the first few days of life, bleeding disorders, jaundice, respiratory and cardiac disease, infections, and fits. There are seven short chapters on metabolic problems and others on necrotising enterocolitis, genitourinary disorders, hydrops, and the floppy infant. Finally, there are sections on practical procedures, social problems, and talking to the parents. In all there are 34 chapters but there are some surprising inconsistencies. There is, for example, an appendix on Apt's test but none on normal laboratory values or on drug prescribing.

Each chapter describes how the particular condition presents as an emergency, its causes, and how it should be investigated and managed, with selected references and bibliography for further reading. Inevitably, many of the conditions described are not actual emergencies, but problems needing prompt attention and hence my comment that this is more a textbook on acute neonatology than a senior house officer's pocket book of neonatal intensive care.

I no longer have my original copy of the first edition, but I am delighted to have the new one I am sure it will find a place in most special care baby units and that the nurses and senior house officers will find it a very readable and useful guide, but I suspect that the authors have 'missed the boat' and that it won't displace the competition.

On a personal note, there is an awful lot of bicarbonate being recommended for use in this book, isn't it about time paediatricians outgrew their addiction to this stuff?

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Consultant paediatrician

Neonatal Infections. David Isaacs and E Richard Moxon. (Pp 256; £35 hardback.) Butterworth-Heineman Ltd, 1991. ISBN 0-7506-1319-X.

In a week when every child on our neonatal intensive care unit has had one, and in some cases even two, infection screens, it seems appropriate to sit down and review this text on neonatal infections. Dr Isaacs and Professor Moxon do not set out to provide a discursive and complete text, but more one that discusses the principles and thought processes behind the management of perinatal and neonatal infections. Its success or failure must depend upon the frequency with which one uses it as a reference and as a starting point to broaden one's academic base

The book starts with three chapters covering background, epidemiology, pathogenesis, and immunity. These chapters are brief, tightly written, and interesting. Thereafter follow chapters on the clinical aspects of infection, its presentation, investigation, and policies for using antibiotics and general support One of the delights of reading these chapters is the commonsense approach that is taken to many issues which cause dissention and arguments on neonatal ward rounds Next are useful chapters on specific clinical infection groups and then specific infective agents. Finally, this comprehensive text takes up the issues of surveillance, prevention, and clinical pharmacology

As a book it has immense breadth and depth and sits nicely in a slot in which there is no comparable text The references are well made and up to date and I think this provides the first good UK text on the subject. It also emphasises the importance of good infectious disease input on the neonatal unit. It will be of value for all grades of neonatal staff from consultant to neonatal nurse.

For such a subject where each neonatal paediatrician has his own series of solutions, I found the commonsense approach that the authors have taken left me with very few areas of disagreement. Two niggles might be that it is sad to see that 'TORCH' is still alive after its recent press and the picture of a 'card index file' was utterly rivetting!

In short an excellent text which I am sure will soon take up residence on every neonatal unit.

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Would a cytomegalovirus vaccine prevent congenital infection?

Estimates of the incidence of intrauterine infection with cytomegalovirus have varied between about 0·5 and 2·5% of live births. Only some 10% of babies so infected are symptomatic at birth but of the remaining 90% between 5 and 20% will subsequently show a neurological deficit.

Cytomegalovirus infection differs from rubella and toxoplasma in that the maternal infection does not necessarily occur during or immediately before the pregnancy but the fetus is still at risk from maternal infection acquired even years before. That being so, do maternal antibodies give any protection to the fetus and would a vaccine be of any use? A paper from Birmingham, Alabama (Karen B Fowler and colleagues, *New England Journal of Medicine,* 1992;**326:**663–7) attempts to answer these questions.

Congenital cytomegalovirus infection was diagnosed in 197 babies by isolating the virus from urine in the newborn period. Of these 197, infection was thought to have occurred during or immediately before the pregnancy in 132 mothers (primary infection) and some considerable time before in the remaining 65 (recurrent infection). Primary infection was diagnosed if either seroconversion was demonstrated during pregnancy (or since the last pregnancy) or IgM antibodies to cytomegalovirus were detected in maternal serum. When no IgM antibodies were found or the mother was known to have had antibodies previously the infection was assumed to be recurrent.

Symptomatic cytomegalovirus infection in the newborn, most commonly with jaundice, petechiae, or hepatosplenomegaly, only happened with primary maternal infection and was seen in 24 of 132 (18%) such cases. One hundred and eighty nine children were followed up for a mean of nearly five years and neurological sequelae were found in 25% after primary infection and 8% after recurrent infection. Sensorineural hearing loss was detected in 15% of the 'primary' group and 5% of the 'recurrent' group but none in the 'recurrent' group had bilateral loss or a speech threshold of 60 dB or more whereas each of these deficits occurred in 8% of the 'primary' group. Similarly no child in the 'recurrent' group suffered from mental retardation (IQ≤70), epilepsy, or cerebral palsy but in the 'primary' group 13, 5, and 1% of children were so affected. Chorioretinitis was seen in seven of 112 (6%) in the primary group and one of 54 examined (2%) in the 'recurrent' group while microcephaly occurred in 5% and 2% respectively. Three babies died, all after primary infection.

Although the methods used in this study to distinguish between primary and recurrent infection are not completely reliable, there seems little doubt that an effective vaccine against cytomegalovirus would give considerable, though not complete, protection against damage from intrauterine infection. In an editorial in the same issue (pages 702–3) Martha Yow and Gail Demmler of the Baylor College of Medicine in Houston discuss the pros and cons of the live attenuated vaccine (Towne 125), which was developed in 1975, and possible new vaccines based on virus subunits, but call for a national vaccination programme to be set up without much further delay. In their words: 'We should not wait another 20 years while thousands of additional children are born seriously handicapped'.

ARCHIVIST

PS. A paper in the *Pediatric Infectious Disease Journal* from the same teams in Birmingham, Alabama (Suresh B Boppana and colleagues, 1992;**11:**93–9) gives details of the dreadful toll of symptomatic congenital cytomegalovirus infection in 106 newborn babies.

Archives of Disease in Childhood 1992; 67: 889–891

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The Journal of the British Paediatric Association

Annotations

Angelman's syndrome

Angelman's syndrome is one of the causes of severe mental handicap that is associated with a characteristic facial and behavioural phenotype. It was first described by Harry Angelman in 1965[1] and was reported only infrequently in the literature up until 1987 when a proportion of patients with the syndrome were noted to have a small deletion of the long arm of chromosome 15 at 15q11–13.[2 3] Since then interest in Angelman's syndrome has grown, leading to an increased frequency of diagnosis and greater awareness of the clinical features of this condition.[4]

Clinical history

The infant with Angelman's syndrome is usually born after a normal pregnancy and the birth weight is approximately 200 g less than normal siblings. In the neonatal period feeding problems are common, with difficulty in establishing breast feeding, gastro-oesophageal reflux, and poor weight gain even though the infant appears to suckle for long periods. The babies are often tremulous on handling and frequent jerky movements become apparent during the first months of life. Smiling begins at the normal time but there is a delay in motor milestones with inability to sit unsupported until around 12 months. There is appreciable truncal hypotonia but in contrast the limbs are usually stiff. Crawling is commonly in the 'commando' style and independent walking is generally achieved at around 3 to 4 years, although some children walk as early as 2 years. A minority do not become ambulant, and these children tend to have the greatest degree of limb spasticity or additional problems such as scoliosis or cerebral palsy. The gait in Angelman's syndrome is characteristically ataxic with a wide base and stiff legs. The arms are upheld and flexed at the elbow, a posture which led to the condition being known as 'happy puppet syndrome'.[5] This name was not popular with parents and other carers and is no longer in common use.

Altogether 80% of patients with Angelman's syndrome suffer from a seizure disorder. The onset of seizures is generally between 18 and 24 months and the first is typically precipitated by a fever. Thereafter seizures may occur at any time and all seizure types are observed with myoclonic jerks and drop attacks being particularly frequent. Infantile spasms have also been reported,[5] but without the finding of hypsarrthymia on the electroencephalogram (EEG). The seizure pattern is often episodic with severe bouts of seizures interspersed with fit free periods of several weeks or months. They may be very difficult to control but sodium valproate and clonazepam appear to be the most effective anticonvulsants. The EEG appearances are striking and have been described by Boyd *et al*,[6] who noted several characteristic features, the most consistent of which was posterior slow wave activity with discharges, facilitated by or seen only on passive eye closure. The authors emphasised that more than one EEG may be needed to demonstrate the typical appearances. The changes are also age dependent, being less florid in the older children and reflecting the clinical findings, as seizures become less frequent in later childhood and may cease altogether. Computed tomograms are usually normal or show only mild ventricular dilatation and cerebral atrophy.

Children with Angelman's syndrome are unable to acquire more than two or three words of speech and must communicate by sign language or primitive gestures. The ability to acquire sign language varies but only a minority will have no means of communication. Comprehension skills appear to be significantly better than those of expressive speech. It is difficult to test accurately the level of cognitive functioning in this group of children who have specific problems with both speech and coordination but they fall within the educationally subnormal group.

Facial phenotype

The dysmorphic facial features in Angelman's syndrome are subtle and evolve with age, becoming more apparent from the second year of life. The head circumference falls within the lower half of the normal range, although only 25% are truly microcephalic. The skull is usually brachycephalic and there may be a horizontal groove in the skull just above the occiput. The mouth is typically wide and smiling and the upper lip is thin. The chin is pointed and prominent and the tongue protrudes between the wide spaced teeth. Approximately half of the children have fair hair and skin and most have blue eyes; 40% have an alternating strabismus. Fundoscopy in the more hypopigmented children reveals deficient choroidal pigmentation,[7] but this rarely affects the visual acuity.

Behavioural phenotype

Behavioural features provide the clue to diagnosis in younger children where dysmorphic facial features are not apparent, especially if the familial features are prominent. These children have a happy, sociable affect and laugh frequently, and sometimes inappropriately, for example on venepuncture. The laughter is not uncontrollable, however, and is always provoked, even though the stimulus may be minimal. It is not related to electrical activity within the brain as in gelastic epilepsy. In association with the laughter there is a tendency to flap the hands when excited. Other characteristic behaviours include a love of water, reflections, and noises.

Natural history

General health in Angelman's syndrome is good and there are no major life threatening physical problems. Scoliosis occurs in 10% of patients and is usually recognisable early in life and amenable to treatment by bracing, although some patients require surgery particularly if the scoliosis worsens at adolescence. Most patients remain mobile if they have regular exercise to prevent the development of contractures in their hypertonic limbs. After the hyperactivity of childhood the behaviour of older children is quieter and seizures absent or easier to control. The majority of patients will develop some self help skills and be able to feed themselves, toilet themselves by day, dress with help, and perform simple household tasks.[8] No patient with Angelman's syndrome has been able to live independently.

Genetics of Angelman's syndrome

Angelman's syndrome arises as the end result of several different genetic mechanisms. Most cases are sporadic within a family but several families have been reported where there has been more than one affected child.[9–11] Around 60% of patients have a *de novo* deletion of chromosome 15q11–13 which is visible cytogenetically.[12] This deletion is in exactly the same place as that known to be associated with Prader-Willi syndrome.[13] The two conditions have distinct clinical phenotypes and although some minor features are common to both, such as fair hair colouring and blue eyes, the major clinical features do not overlap.[14] The parents' chromosomes are normal but in Angelman's syndrome the deletion always arises on the chromosome 15 which has been inherited from the mother and in Prader-Willi syndrome this same deletion is paternally derived.[15] Angelman's syndrome and Prader-Willi syndrome therefore provide a perfect human model for genomic imprinting, the phenomenon whereby genetic information is expressed differently depending on the parent of origin.[16] In a further 15% of families with Angelman's syndrome, though there is no apparent cytogenetic deletion, a deletion of 15q11–13 can be detected on DNA analysis.[17]

Two to three per cent of patients have inherited both of their chromosome 15s from a single parent, and are therefore said to have uniparental disomy for chromosome 15.[13] There are no deletions and both the 15s come from the father. It is likely that the conceptus was originally trisomic for chromosome 15 and that the maternal 15 was lost during the early cell divisions in order for the embryo to remain viable. In both uniparental disomy cases and those with a *de novo* chromosome 15 deletion parental chromosomes are normal and recurrence risks are judged to be low.

In around 5% of families there is a chromosomal rearrangement in the mother—for example an inversion or translocation which can give rise to Angelman's syndrome when passed to a child because of the predisposition to deletion of 15q11–13.[19] There is a risk to subsequent children and possibly other family members and so it is wise to check parental chromosomes in all cases of Angelman's syndrome in order to rule out this situation.

In the remaining families, around 15%, there is no evidence of a typical 15q11–13 deletion or of uniparental disomy using either cytogenetic or molecular genetic techniques. This is the group with the highest risk of recurrence because, to date, all families with more than one affected child fall into this category. Current research suggests that the affected siblings may be inheriting a small mutation that came from one of the mother's chromosome 15s. Familial Angelman's syndrome is therefore likely to have an autosomal dominant mode of inheritance with a 50% recurrence risk. Angelman's syndrome will only result, however, if the mutation is maternally transmitted because of the phenomenon of genomic imprinting. This theory is supported by recent work from Japan.[20]

It is clear that the 15q11–13 region contains not one but several different genes and further molecular studies are now in progress to identify and sequence these genes. The gene for the GABA receptor β 3 subunit was recently localised to 15q11–13 for example.[21] Lack of normal functioning of this gene could be relevant to the occurrence of seizures and hyperactivity and to the effectiveness of sodium valproate treatment. Investigations of gene expression may in due course provide an explanation for the symptomatology in Angelman's and Prader-Willi syndromes, a guide to treatment for these symptoms, and a clue to the mechanisms responsible for genomic imprinting in man.

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Archives of Disease in Childhood 1992; 67: 891

Psychological treatments for childhood asthma

A recent review of the social and emotional impact of childhood asthma noted four main categories: social and leisure pursuits, schooling, practical aspects of daily life, and emotional effects.[1] A fifth, and perhaps the most important, is the vicious cycle between the emotional and social impact on the child and family and the course of the asthma.

Parental denial or overprotectiveness, inappropriate handling of the asthma, family tensions or conflict, and the child's emotional reactions to the asthma can each exacerbate the illness as a result of, separately or in combination, emotional arousal, suggestion, conditioning, or hyperventilation.[2 3] Various psychophysiological processes have been proposed including increased vagal activity, raised endogenous adrenal steroid output, and central nervous system mechanisms such as the hypothalamic-limbic-midbrain circuits that can influence the immune systems and produce tissue change.[3 4]

There is therefore an obvious rationale for taking a comprehensive approach to the assessment and treatment of childhood asthma. The essence of such an approach is to give due consideration to physical, psychological, and social factors both in assessment and management. The emotional reactions to and social consequences of the asthma for both child and family should be specifically explored and discussed. Possible emotional and social triggers should be sought, and both short term and long term reactions to attacks explored. This allows not only for identification of problems, with the potential for resolution of at least some of them, but also for expression of feelings which, if remaining suppressed, may exacerbate the illness. Discussion of the emotional, financial, and practical burden of the asthma helps parents and children feel better understood, promotes confidence and trust, and encourages compliance. Anxieties which might otherwise exacerbate the illness can in this way be resolved.

After a comprehensive assessment a clearly defined and goal oriented management plan can be formulated. This will include both physical and psychological treatments. The most useful psychological approaches include parental counselling, family therapy, and behavioural treatments.

Parental counselling focuses on helping the parents to work together, supporting and helping each other in their management of the asthma, sharing problems and decisions, identifying and resolving conflicts, and remaining consistent between each other and over time. Single parents can be helped to identify problem areas and to seek solutions, as well as to find support within their own community.

The aim of family therapy is to help modify the dysfunctional aspects of family relationships so that the asthma is neither maintained nor exacerbated by them. Particular areas of attention include (a) helping adopt more realistic attitudes to the illness, (b) moving away from overinvolvement and overprotectiveness or denial, (c) promoting age appropriate behaviour in the child, and particularly in relation to looking after the asthma, and (d) promoting open and direct communication, thus allowing for the expression and acknowledgement of distress and the identification and resolution of conflict, especially where this involves the asthmatic child. A number of studies have demonstrated the value of family therapy in childhood asthma.[5–7]

Behavioural treatments include relaxation, systematic desensitisation, and biofeedback. Self relaxation is of particular value when anxiety levels are high and can be taught to most children aged 7 upwards in a few minutes. Voluntary muscle relaxation is accompanied by concomitant relaxation of bronchial smooth muscle and subsequent relief of symptoms.[8] This process can be enhanced by the use of systematic desensitisation.[9] Children are taught to identify psychological triggers (for example, angry mother, teasing, etc) and then in a state of relaxation imagine themselves exposed to each in turn. The aim is to help the child remain relaxed while imagining the threatening situation. Most children can carry over the technique in vivo. The use of biofeedback equipment is enjoyed by children, assists the learning of these techniques, and has been shown to reduce the need for steroids.[10] Cognitive approaches may also be used and involve helping children gain mastery over situations in which they feel fearful or helpless.

A specific psychological intervention is indicated when there is:

(a) an obvious trigger for the asthma,
(b) clear evidence of behavioural or emotional disturbance,
(c) clear evidence of family dysfunction, such as disturbed relationships, or inappropriate handling of the illness,
(d) school based difficulties,
(e) failure of standard treatment or steroids are required,
(f) non-compliance with medication.

Paediatricians cannot be expected to have either the time or expertise to offer all of these treatments but basic skills in parental counselling are essential. Given the relevance of psychosocial factors in childhood asthma, every effort should be made to ensure ready access to a child psychologist or psychiatrist who can offer some of the other treatments outlined.

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Archives of Disease in Childhood 1992; 67: 892–899

ORIGINAL ARTICLES

Cryptorchidism: a prospective study of 7500 consecutive male births, 1984–8

John Radcliffe Hospital Cryptorchidism Study Group[1]

Abstract

A total of 7441 boys were examined for cryptorchidism at birth and, if present, again at 3 months of age. After excluding boys with severe congenital malformations noted at birth, the cryptorchidism rates at 3 months in babies weighing <2000 g, 2000–2499 g, and ≥2500 g were 7·7%, 2·5%, and 1·41% respectively. The overall rate was 1·55%. The cryptorchidism rate at birth had increased by 35·1% and at 3 months by 92·7%, over Scorer's rates in the 1950s. Part of these increases may be attributable to differences in neonatal mortality, but the increases in babies weighing 2500 g or more of 50·2% at birth and 77·4% at 3 months are unlikely to be overestimates. At birth 1·92% of boys had bilateral cryptorchidism and 3·0% unilateral cryptorchidism. Boys with cryptorchidism at 3 months were more likely to have hypospadias, a small scrotum, and poor scrotal rugation compared with boys having normally descended testes at birth. Factors predicting descent by 3 months in babies cryptorchid at birth are birth weight, laterality and scrotal size, babies with low birth weight, bilateral cryptorchidism, and normal scrotal size being more likely to have normally descended testes by 3 months. Descent by 3 months was more likely the lower the testis along the normal pathway of descent. The orchidopexy rate at an average age of 3 years was 1·24%. This is substantially lower than in other series and lower than our estimated rate of 2·9% using Hospital In-Patient Enquiry data for England and Wales.

Some 10% of patients with testicular cancer have a history of cryptorchidism, and epidemiological evidence suggests that there are underlying factors common to both conditions.[1] Undescended testis is also closely associated with infertility.[1 2] Neither the extent of the risk of testicular cancer nor the extent of infertility appears to be affected by correcting the cryptorchidism.[1–3] Cryptorchidism is thus an important congenital defect, and there is evidence from data on orchidopexy rates from the Hospital In-Patient Enquiry for England and Wales that its incidence may have doubled between 1965 and 1985.[4] This increase in orchidopexy rates may, however, only demonstrate that boys with retractile rather than truly cryptorchid testes are being operated on, possibly unnecessarily.

In a study in the late 1950s of over 3000 babies delivered in a hospital in west London and followed up to 1 year of age, Scorer found that the incidence of undescended testis was about 0·8%.[5] We have examined a four year cohort of babies born between 1984 and 1988 in order to discover whether the incidence of undescended testis has changed since the late 1950s, and to investigate risk factors for the condition. A preliminary report on the incidence findings for the subcohort born between November 1984 and October 1985 has been published.[6] This paper describes the incidence findings in the complete four year cohort.

Subjects and methods

Full details of subjects and methods have been previously described.[6] An abbreviated description including the essential information is given here.

All babies born between 1 November 1984 and 31 October 1988 to mothers resident in a defined area (the study area) within the boundaries of the Oxfordshire Health Authority were included in the study. Almost all (98·2%) of the babies were born in the John Radcliffe Hospital, Oxford.

EXAMINATION

In addition to the usual examination by paediatric staff, each boy born in the John Radcliffe Hospital was examined for cryptorchidism during the first 24 hours of life by one of four specially trained research nurses. Special attention was paid to standardising the examination technique. The position of the testis in the scrotum was noted after manipulation of the testis into the lowest position along the pathway of normal anatomical descent without tension being applied. The position of each testis was classified as follows: normal (well down in the scrotum), high scrotal, suprascrotal (palpable, in the line of normal descent including the inguinal pouch, but not in the scrotum), non-palpable, and 'other'—ectopic, neonatal orchidopexy (that is, during the first few days of life) before examination, position obscured by hernia or hydrocoele, and scrotum too badly bruised following breech delivery to be certain of position. This classification forms the basis of our definition of 'undescended testis by position' with all except testes well down in the scrotum being classified as undescended by this definition.

In order to compare our results with those of Scorer[5] we also attempted, in consultation with both paediatricians and paediatric surgeons, to reproduce exactly his technique of examination and classification.[7] A testis was classified as 'cryptorchid by measurement' if the centre of

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Accepted 9 March 1992

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the testis was less than 4 cm below the pubic tubercle (2·5 cm at the birth examination for babies weighing under 2500 g). All measurements were rounded down to the nearest 0·5 cm. Measurement was made, as above, after manipulation of the testis into the lowest position along the pathway of normal anatomical descent without tension being applied. This definition of undescended testis is precisely that adopted by Scorer.[5]

Boys admitted to the special care nursery were examined as soon after birth as their medical condition allowed. Non-white babies and babies whose mothers either did not speak English or had a severe psychotic illness were not examined as part of this study. In practice we attempted to examine all boys born at the hospital. If a boy with cryptorchidism was found who was for any reason ineligible for the study, the general practitioner was informed and asked to arrange further follow up. These cases are not considered further here.

Boys cryptorchid at birth by either definition were examined at home by one of the four research nurses 3 months after their expected date of delivery. At this 3 month visit the boy was re-examined as above; if after manipulation a testis was still undescended by either definition the boy was referred to a special paediatric surgical outpatient clinic for final assessment. This assessment was made using the criterion that a descended testis must be able to be manipulated into the bottom of the scrotum and remain there without tension being applied—that is, the same definition as cryptorchid by position.

Babies born in the John Radcliffe Hospital who were not examined at birth were examined at home 3 months after their expected date of delivery, as were those boys born outside the hospital who were resident within the study area. At 3 months of age a sample of 393 babies with normally descended testes at birth were also re-examined.

In all except table 2 and table 5, the assessment of the testes is by position at birth and by final assessment at the paediatric clinic at 3 months. In table 2, which compares Scorer's data with ours,[5] the testes are assessed by measurement. A few babies (n=13) had already had an orchidopexy by 3 months; these babies were assumed to be cryptorchid by position and by Scorer's definition at 3 months. All 13 boys had been examined at birth and 12 were cryptorchid at birth by either definition; measurements were not recorded for one baby with a torted testis operated on within 24 hours of birth and this baby is treated as cryptorchid at birth also.

STATISTICAL METHODS

Differences in binomial proportions (2×2 tables) were tested for statistical significance (p values) by Fisher's exact test.[8] The method of Mantel and Haenszel was used for testing the joint statistical significance of differences in proportions in multiple 2×2 tables.[8] Quoted p values are one sided unless otherwise noted; p values are one sided for comparison of cryptorchidism rates over time; as the question posed before the study was whether the rate of cryptorchidism had increased. Approximate confidence limits for the adjusted overall proportion of cryptorchid boys at the 3 month examination were calculated assuming large sample normality with the separate variances of the birthweight specific proportions estimated in the standard manner.

In order to compare our cryptorchidism rates with those reported by Scorer for the 1950s,[5] both sets of rates were adjusted to the 1980 birthweight distribution[9] as described in Chilvers and Pike.[1]

The method of Walter and Elwood was used to test for seasonal variation in rates of cryptorchidism by month of birth.[10]

Results

INCIDENCE

A total of 7733 eligible boys were born alive in the study area in the 48 months of the study; 7594 (98·2%) of them in the John Radcliffe Hospital, and 7441 (96·2% of eligible boys, and 98·0% of the eligible boys born in the John Radcliffe Hospital) were examined soon after birth (at-birth examination). One hundred and fifty three eligible babies born in the John Radcliffe Hospital were thus not examined at birth: 25 mothers refused permission for their babies to be examined, three mothers were too ill to give consent, 18 babies died, two ill babies were moved to another hospital, and an additional 105 babies left the hospital before being examined.

Forty one of the 7441 boys examined at birth

Table 1 Results of screening for neonatal undescended testis: boys examined in the John Radcliffe Hospital, November 1984 to October 1988

Birth weight (g)	*No examined at birth*	*Cryptorchid**			
		At birth		*At 3 months*	
		No	*Rate (%)*	*No*	*Rate (%)*
(a) Excluding boys with severe congenital abnormalities noted at birth.					
<2000	130	59	45·4	10	7·7†
2000–2499	238	32	13·4	6	2·5
≥2500	7032	270	3·8	99	1·41‡
Total	7400	361	4·9	115	1·55
(b) Including boys with severe congenital abnormalities noted at birth					
<2000	134	63	47·0	10	7·5§
2000–2499	246	37	15·0	8	3·3‖
≥2500	7061	276	3·9	100	1·42¶
Total	7441	376	5·1	118	1·59

*Cryptorchid by position: cryptorchidism present at 3 months decided at special paediatric surgical outpatient clinic

†Two boys declared by their general practitioner as having descended testes assumed to have descended testes by our criteria

‡One boy who left the area assumed to have descended testes and four boys declared by their general practitioner as having descended testes assumed to have descended testes by our criteria

§Two boys declared by their general practitioner as having descended testes and three boys with severe congenital abnormalities assumed to have descended testes by our criteria (see text).

‖Two boys with severe congenital abnormalities assumed to have descended testes by our criteria (see text)

¶One boy who left the area assumed to have descended testes, four boys declared by their general practitioner as having descended testes, and one boy with a severe congenital abnormality assumed to have descended testes by our criteria (see text) were known at the time of our initial examination to have a severe congenital malformation (described later). Of the 7400 remaining boys examined at birth, 361 (4·9%) were found to have one or both testes undescended by position; table 1a shows the results of this examination by the birth weight of the babies. Fifty nine (45·4%) of the 130 babies weighing less than 2000 g were cryptorchid, as were 32 (13·4%) of the 238 babies weighing between 2000 and 2499 g, and 270 (3·3%) of the 7032 babies weighing 2500 g or more. At 3 months of age 354 (98·1%) of the 361 boys who were born in the John Radcliffe Hospital and found to have an undescended testis at birth were re-examined (the families of four of the remaining babies withdrew consent for further examination, one family had moved away, and two mothers were educationally subnormal and were not reapproached); 115 were found to be cryptorchid after examination at the special clinic (3 month examination; table 1a). The general practitioners or health visitors, or both, of the six families who either withdrew permission at 3 months or where the mother was educationally subnormal, reported that the testes of all six babies had descended since leaving hospital. The cryptorchidism rate at 3 months (table 1a) was calculated on the assumption that all seven boys not examined by us at 3 months had descended testes. The overall cryptorchidism rate had declined to 1·55% (115/7400): 7·7% (10/130) in boys weighing less than 2000 g at birth, 2·5% (6/238) in boys weighing between 2000 and 2499 g, and 1·41% (99/7032) in boys born weighing 2500 g or more. After further subdivision into seven groups by birth weight (<1000 g, 1000–1499, etc to ≥3500), tests for trend in cryptorchidism rates by birth weight were highly significant (at birth: $\chi^2_1=312\ 3$, $p<0·0001$; at 3 months $\chi^2_1=9·2$, $p=0·002$). Table 1b includes babies with severe congenital malformations: the cryptorchidism rate at 3 months increases from 1·55% to 1·59%.

We also examined at 3 months of age 98 (93·3%) of the 105 babies who were born in the John Radcliffe Hospital but who left the hospital before being examined, and 121 (87·1%) of the 139 babies born outside the hospital. (None of these 244 babies had a severe congenital abnormality and all weighed more than 2500 g at birth.) The families of the remaining seven babies born in the John Radcliffe Hospital had moved away. Of the remaining 18 babies born outside the hospital four had moved away, and the families of 14 refused consent for examination. All 25 babies were reported as having descended testes by their general practitioners; these babies are assumed to have descended testes at 3 months. A total of 7644 babies without a severe congenital abnormality noted at birth, 99·4% of the 7692 such babies eligible for the study, were thus effectively screened at 3 months of age and 116 (1·52%) had an undescended testis. The cryptorchidism rates in babies weighing less than 2000 g, 2000–2499 g, and 2500 g or more at birth were 7·7% (10/130), 2·5% (6/238), and 1·37% (100/7276) respectively; these results are virtually identical with those in table 1a.

Table 2 Comparison of rate (%) of cryptorchidism found at screening by Scorer (circa 1955) and in boys examined at the John Radcliffe Hospital†*

Screening examination and birth weight (g)	*Scorer‡*	*Present study‡*	*Increase§*
At birth:			
<2500	21·0 (63/300)	22 8 (84/368)	8·7
≥2500	2·7 (90/3312)	4·1 (287/7032)	50·2
All	4 2 (153/3612)	5·0 (371/7400)	18·4
Adjusted‖	4·0 (3·4 to 4 6)	5·4 (4·8 to 5·9)	35·1
At 3 months			
<2500	1·74 (5/288)	5·2 (19/368)	197 4
≥2500	0·91 (30/3312)	1·61 (113/7032)	77·4
All	0·97 (35/3600)	1·78 (132/7400)	83 5
Adjusted‖	0·96 (0·64 to 1·28)	1·85 (1·53 to 2·2)	92 7

*Cryptorchid by measurement.

†Excluding boys with severe congenital abnormalities noted at birth.

‡Figures in parentheses are: number of babies with an undescended testis/number examined.

§Increase in rate from Scorer to present study.

‖Adjusted to the 1980 national birthweight distribution (95% confidence intervals)

COMPARISON WITH 1950'S RATES

For comparison with the rates reported by Scorer, cryptorchidism must be defined in terms of measurement (see methods). Table 2 shows our results by measurement; nine babies had the position of their testes noted at birth but no measurement of the testes were recorded. All nine had descended testes by position and we have made the most probable assumption that they had descended testes by measurement. This assumption also ensures that we have not biased our results upwards. Babies who had an orchidopexy before measurement at birth or at 3 months are assumed to be cryptorchid by measurement. The babies not measured at 3 months but reported either by the research nurses or their general practitioner or health visitor to have descended testes are assumed to have measurements greater than 4 cm; this assumption again ensures that we have not biased our results upwards. Babies with measurements greater than 4 cm (or 2·5 cm in those weighing less than 2500 g) at birth were assumed to have normally descended testes at 3 months as would have been the case in Scorer's study.[5] The criteria used for definition of cryptorchidism are precisely those adopted by Scorer[5] and the numbers for the John Radcliffe Hospital do not agree completely with those in table 1a. The overall incidence of cryptorchidism by measurement at birth (adjusted to the 1980 national birthweight distribution) has increased from 4·0% to 5·4% (an increase of 35·1%, p=0·0006) since the mid-1950s: an 8·7% increase in babies weighing less than 2500 g at birth and a 50·2% increase in heavier babies. At 3 months of age the adjusted rate has increased from 0·96% to 1·85%, an increase of 92·7% (p=0·0002): a 197·4% increase in babies weighing less than 2500 g and a 77·4% increase in heavier babies.

BOYS WITH SEVERE CONGENITAL MALFORMATIONS AT BIRTH

As noted above, 41 boys identified at birth as having severe congenital abnormalities were

Table 3 Results of 3 month examination for undescended testes by birth weight and whether unilateral or bilateral: all boys examined in the John Radcliffe Hospital, November 1984 to October 1988[*]

Birth weight (g)	No examined	No of bilateral undescended testes at birth			Proportion descended (%)†	No of unilateral undescended testes at birth			Proportion descended (%)†
		At birth	Unilateral at 3 months	Bilateral at 3 months		At birth	Unilateral at 3 months	Bilateral at 3 months (%)†	
<2000	130	40	4	2	85·0	19	3	1	79 0
2000–2499	238	11	1	0	90 9	21	4	1	76·2
≥2500	7032	91	12	13	72 5	179	71	3	58·7
Total	7400	142 (1·92%)	17 (0 23%)	15 (0 20%)	77 5‡	219 (3·0%)	78 (1 05%)	5 (0 07%)	62 1‡

[*] Excluding boys with severe congenital abnormalities noted at birth.

†Percentage of boys with undescended testes at birth whose testes were descended at 3 months

‡Test for difference in proportions of bilateral and unilateral undescended testes at birth whose testes were descended at 3 months, adjusted for birth weight: $\chi^2_1=5\cdot5$, two sided p=0·02

born alive at the John Radcliffe Hospital during the study period. This will be an underestimate of the total number of major malformations as some, for example congenital heart disease, may only be apparent some time after birth. These 41 babies are excluded from all tables except table 1b. All 41 babies were examined at birth and nine of the 15 found to be cryptorchid at birth were examined at 3 months. The family situation of the six babies who were cryptorchid at birth who were not examined at 3 months was such that further examination could not be justified. In table 1b these are assumed to be descended. Thirty three babies had malformations which are almost certainly identifiable at birth and may be regarded as a complete ascertainment. The incidence of cryptorchidism at birth in this group is 42·4% (14/33), clearly significantly greater than in boys without such congenital malformations. Their incidence of cryptorchidism at 3 months (at least 6·1% (2/33)) is also increased. A second group of eight babies had abnormalities many of which may be missed at birth: for those whose malformations were recognised at birth, the cryptorchidism rate both at birth and at 3 months is 12·5% (1/8).

LATERALITY

Of the 7400 boys without a severe congenital malformation born in the John Radcliffe Hospital, 142 (1·92%) had bilateral cryptorchidism at birth and 219 (3·0%) unilateral cryptorchidism at birth (table 3). In the latter group 52·1% (114/219) had left sided and 47·9% (105/219) right sided cryptorchidism. In each birthweight category the proportion descending by 3 months was greater for babies with bilateral cryptorchidism at birth than for babies with unilateral cryptorchidism at birth. At 3 months of age the bilateral cryptorchidism rate was 0·27% ((15+5)/7400) and the unilateral cryptorchidism rate was 1·28% ((17+78)/7400). Of the 95 babies with unilateral cryptorchidism at 3 months 50·5% (48/95) had left sided and 49·5% (47/95) right sided cryptorchidism. At 3 months of age 77·5% (110/142) of those with bilateral cryptorchidism at birth and 62·1% (136/219) of those with unilateral cryptorchidism at birth had descended testes (test for difference in proportions descending adjusting for birth weight: two sided p=0·02). Of the 142 babies with bilateral cryptorchidism at birth, 12·0% (17/142) had one undescended testis at 3 months while 10·6% (15/142) still had bilateral cryptorchidism. It should be noted that 2·3% (5/219) of the babies with unilateral cryptorchidism at birth had bilateral cryptorchidism at 3 months.

OTHER ABNORMALITIES OF GENITALIA

The relationship between cryptorchidism and other abnormalities of the genitalia is shown in table 4. In a few instances the examination was incomplete; in these cases it has been assumed that the babies were normal. Although few hernias were noted at birth (two out of the 7039 babies whose testes were descended, none of the 246 with late descending testes, and four of the 115 babies cryptorchid at 3 months), by 3 months of age 5·0% (12/238) of boys with late descending testes examined at 3 months, 13·9% (16/115) of boys cryptorchid at 3 months and 1·27% (5/393) of control babies examined at 3 months had a hernia. Although hydrocoeles appear to be related to late descending testes there is no apparent relationship with cryptorchidism at 3 months. There is a clear relationship between hypospadias and cryptorchidism: three times as many cryptorchid babies had hypospadias than those with normally descended testes (5·2% (6/115) *v* 1·56% (110/7039), p<0·05). The scrotum was observed to be small in 43·1% (106/246) of boys cryptorchid at birth only and in 55·7% (64/115) of boys cryptorchid at 3 months (both p<0·05, two sided tests, for comparison with boys with normally descended testes). Scrotal rugation was described as poor more often in boys with undescended (8·7%) or late descending (5·7%) testes than in boys with normally descended testes (0·14%) (both p<0·05).

Table 4 Relationship between cryptorchidism and other characteristics recorded at birth: boys examined at John Radcliffe Hospital.[*] *Results are number (%)*

	Descended (n=7039)	Undescended	
		At birth only (n=246)	At 3 months (n=115)
Hernia	2 (0 03)	0 (0)	4†§ (3·5)
Hydrocoele	599 (8·5)	35‡ (14·2)	7† (6 1)
Hypospadias	110 (1 56)	6 (2 4)	6§ (5 2)
Small scrotum	251 (3·6)	106‡ (43 1)	64†§ (55·7)
Poor scrotal rugation	10 (0 14)	14‡ (5 7)	10§ (8 7)

[*] Excluding boys with severe congenital abnormalities at birth

†Two sided p<0·05 for difference between those undescended at birth only compared with those undescended at 3 months.

‡Two sided p<0·05 for difference between those descended at birth compared with those undescended at birth only.

§Two sided p<0·05 for difference between those descended at birth compared with those undescended at 3 months

Table 5 Proportion of boys examined at the John Radcliffe Hospital with undescended testes at birth whose testes were still undescended at 3 months by assessment at the special paediatric clinic by birth weight and measurement and position at birth. Results are undescended testes at 3 months/undescended testes at birth (%)[1]

Birth weight (g)	*Measurement of worst testis at birth (cm)*	*Position of worst testis at birth*					
		Normal	*High scrotal*	*Suprascrotal*	*Not palpable*	*Other*	*Total*
<2500	0	-/-	-/-	6/30 (20·0)	6/12 (50·0)	1/2 (50·0)	13/44 (29·5)
	<2·5	0/4	2/26 (7·7)	1/10 (10·0)	-/-	0/0	3/40 (7·5)
	≥2·5	-/-	0/10	0/1	-/-	0/0	0/11
	Total	0/4	2/36 (5·6)	7/41 (17·1)	6/12 (50·0)	1/2 (50·0)	16/95 (16·8)
≥2500	0	-/-	-/-	11/30 (36·7)	72/110 (65·5)	4/11 (36·4)	87/151 (57·6)
	<2·5	0/2	1/15 (6·7)	2/30 (6·7)	-/-	1/1 (100·0)	4/48 (8·3)
	2·5–3·5	0/23	8/60 (13·3)	0/5	-/-	0/0	8/88 (9·1)
	≥4·0	-/-	0/8	-/-	-/-	0/0	0/8
	Total	0/25	9/83 (10·8)	13/65 (20·0)	72/110 (65·5)	5/12 (41·7)	99/295 (33·6)

[1]Excluding boys with severe congenital abnormalities noted at birth. Nine babies had measurements missing at birth.

ASSESSMENT OF CRYPTORCHIDISM BY MEASUREMENT, POSITION, AND ASSESSMENT OF SCROTUM

The ascertainment of cryptorchidism was made by position of the testes and by measurement as described and used by Scorer.[5] At birth 19 boys were judged to be cryptorchid by position only, 29 by measurement only, and 342 by both criteria.

Table 5 shows the proportions of boys with undescended testes at birth (judged by measurement or position) whose testes were still undescended at 3 months (judged by assessment of position at the special paediatric clinic). All babies with testes in a normal position had descended testes at 3 months regardless of measurement. High scrotal testes with normal measurements were all descended at 3 months. Those with suprascrotal testes and zero measurement at birth (at or above the pubic tubercle) were less likely to descend than those with a non-zero measurement (71·7% (43/60) *v* 93·5% (43/46)). Impalpable or other testes (ectopic, n=6; neonatal orchidopexy before examination, n=1; position obscured by hernia or hydrocoele, n=3; and scrotum too badly bruised after breech delivery to be certain of position, n=4) were the least likely to descend with 61·8% (84/136) still undescended at 3 months.

Scrotal size is an important predictor of late descent in unilateral cryptorchidism (table 6). Boys with unilateral cryptorchidism at birth who had a small scrotum on one side only, were much less likely to have their testes descend by 3 months than boys who had a scrotum of normal size or a small scrotum on both sides (χ^2_2=14·4, p<0·001). In babies with unilateral cryptorchidism at birth, out of 47 with a small scrotum on one side 46 were on the same side as the undescended testis. There was also some evidence that the testes of babies with bilateral cryptorchidism and a small scrotum were less likely to descend, although the differences were not statistically significant. Scrotal rugation did not predict descent.

Table 6 Proportion of boys examined at the John Radcliffe Hospital with undescended testis at birth whose testes were still undescended at 3 months. Figure are undescended testes at 3 months/undescended testes at birth (%)[1]

	Unilateral undescended testis at birth	*Bilateral undescended testes at birth*
Scrotal size		
Normal	40/128 (31·3)	11/63 (17·5)
Small, one side	29/47 (61·7)	2/4 (50·0)
Small, both sides	14/44 (31·8)	19/75 (25·3)
	χ^2 =14·4, p<0·001	χ^2_2=2·99, p=0·22
Scrotal rugation:		
Normal	78/207 (37·7)	27/130 (20·8)
Poor, one side	4/9 (44·4)	1/1 (100·0)
Poor, both sides	1/3 (33·3)	4/11 (36·4)
	Normal *v* poor χ^2 =0·001, p=0·98	Normal *v* poor Fisher's exact test p=0·20

[1]Excluding boys with severe congenital abnormalities noted at birth

SEASONALITY

The distribution of month of birth of boys with cryptorchidism at 3 months and boys with late descending testes was examined. For cryptorchidism at 3 months there is some heterogeneity between the months (χ^2_{11}=20·3, p=0·04) with higher than expected numbers in January, April, and particularly in September. There is no evidence of a cyclic pattern. There are higher than expected numbers of boys with late descending testes born in November, December, and January. There is evidence of heterogeneity (χ^2_{11}=27·8, p=0·004) and of a cyclic pattern (χ^2_2=11·1, p=0·004).

FOLLOW UP

All babies born in the John Radcliffe Hospital with cryptorchidism confirmed at 3 months have been followed up to July 1989. At that time 73·9% (85/115) of such babies had had an orchidopexy, 16·5% (19/115) were borderline and still under review, and 9·6% (11/115) were considered to have normally descended testes.

At 9 months of age 187 of the 246 babies with late descending testes were re-examined by one of the research nurses. Of the babies examined 38·0% (71/187) had testes that were not fully descended by position. Twelve of these were referred to paediatric surgeons either because the testes could not be manipulated into the scrotum or because considerable tension was necessary in order to do so; three have had orchidopexies, five are still under observation, and four have been discharged.

Four (0·06%) of the 7039 babies with normally descended testes at birth are known to have had an orchidopexy: one had an incarcerated inguinal hernia at 3 months, one had torsion of the right testis at 3 months and had a right orchidectomy and left sided orchidopexy, one had an orchidopexy at 15 months and a small dysplastic testis was found, and one had an orchidopexy at age 3 which, on review, may have been unnecessary.

In total 92 babies (85 cryptorchid at 3 months, three late descenders, and four judged by us to be normal at birth) are known to have had a orchidopexy. The orchidopexy rate is, therefore, 1·24% (92/7400) at average age 3 years.

Discussion

In a previous report we recommended that the diagnosis of cryptorchidism should be made on the basis of position rather than measurement, and noted the close agreement between assessment by measurement and position.[11] The assessment by measurement reported here does, however, allow direct comparison with Scorer's study carried out in the 1950s.[5]

Our results and those of Scorer are not exactly comparable for a number of reasons:

(1) For at least part of the time during which Scorer conducted his study he examined stillbirths[7]; these were apparently almost all low birthweight (<2500 g) babies and their incidence of cryptorchidism was undoubtedly high. Estimates of numbers of stillbirths expected in Scorer's cohort suggest, however, that stillbirths were omitted from later reports.[5 12] We did not examine stillbirths. This would inflate his figures relative to ours. In the 1950s many 'low risk' babies were born at home. This would also inflate Scorer's figures relative to ours.

(2) There was a significant neonatal mortality (12 deaths) in cryptorchid low birthweight babies in Scorer's study population (figures for low birthweight babies not cryptorchid at birth are not given). Scorer's 3 month examination result for low birthweight babies might have been as high as 5·7% ((5+12)/300) if these neonatal deaths had been prevented.

(3) Scorer's results may include babies with severe congenital malformations noted at birth. This would inflate his figures relative to ours.

It appears therefore that we can be relatively confident that the 77·4% increase at 3 months shown in table 2 for babies weighing over 2500 g at birth is well founded, and it may be an underestimate. For lighter babies there may have been no 'biological' increase at all over the period.

The only recent UK series that is comparable in terms of methods of ascertainment is that of Morley and Lucas.[13] They carried out an examination at 18 months of babies weighing less than 1850 g at birth and their figure of 9·9% is higher than our figure of 7·7% at 3 months for slightly larger babies (<2000 g). Other UK studies use routinely collected statistics and report much lower rates. Campbell *et al* using data from the Scottish Morbidity Register reported a rate in neonates of 1·4%,[14] but Boggis and Rowlatt have pointed out that only 1/5 boys having an orchidopexy have cryptorchidism detected at birth.[15] We shall discuss later the possible reasons for the discrepancy between cryptorchidism rates and orchidopexy rates. Swerdlow and Melzer,[16] using data from the England and Wales congenital malformation notification scheme, report a cryptorchidism rate of only 0·13%. The congenital malformation scheme is, however, known to greatly underascertain 'minor' congenital malformations.

Elsewhere, a cryptorchidism rate at birth of 4·1% was reported by Buemann *et al*[17] in Denmark, at 9 months of age a rate of 3·3% was reported in West Germany,[18] and at 5 years of age, a rate of 4·1% was reported in New Zealand.[19] By the age of 9 years 3·7% (16/429) of the New Zealand series had had an orchidopexy.

LATERALITY

At birth 39·3% of babies with cryptorchidism had both testes undescended compared with 17·4% at 3 months. A higher proportion of cryptorchid babies weighing less than 2500 g had bilateral cryptorchidism than of those weighing 2500 g or more, both at birth (56·0% *v* 33·7%) and at 3 months (25·0% *v* 16·2%). Scorer's[12] proportions of babies with bilateral cryptorchidism at birth were higher, 67·4% and 27·5% for premature and full term infants respectively. Morley and Lucas found 42·9% of the low birthweight babies cryptorchid at 18 months in their study to have bilateral cryptorchidism.[13] This figure is consistent with our figure of 30·0% at 3 months for babies weighing less than 2000 g ($p>0·05$), although our numbers are very small. Buemann *et al* reported the proportions of bilaterally cryptorchid babies to be even higher than Scorer's (77·9% in premature babies and 39·0% in full term babies),[17] almost certainly due to differences in examination technique.

We report no difference in the proportions of left sided and right sided cryptorchidism, unlike Scorer who found 64·7% of all unilateral cryptorchidism to be left sided,[12] and Buemann *et al* who reported only 42·5% with left sided cryptorchidism.[17]

CRYPTORCHIDISM AND OTHER ABNORMALITIES

The boys in this study were not routinely followed up for congenital malformations. Thus, only those diagnosed at, or soon after, birth have been considered. Other minor abnormalities are omitted because such conditions would be more likely to be picked up by us in boys cryptorchid at birth because only these boys were followed up routinely in this study. Ascertainment of congenital anomalies unlikely to be found at birth would give biased results. At birth 42·4% of boys with congenital anomalies fully ascertainable at birth had undescended testes. At 3 months the rate is at least 6·1%, but could be as much as 24·2% if all six babies not examined at 6 months were cryptorchid. The association between chromosomal abnormalities and cryptorchidism is well known. Cryptorchidism has been reported to be found in Down's syndrome in between 14% and 27% of cases and in 84% of cases of Prader–Willi syndrome.[20]

We have shown an association between cryptorchidism and inguinal hernia, hydrocoele, hypospadias, and an abnormal scrotum. Having a small scrotum is the commonest, being present in 55·7% of boys cryptorchid at 3 months. Both inguinal hernia and hydrocoele occur as a consequence of incomplete closure of the processus vaginalis.[12] Surgical series report a much higher incidence of inguinal hernia associated with cryptorchidism[21] than that found here. Presumably many are not evident except at surgery. Hjertkvist *et al* report a relative risk of hypospadias of 2·7 (95% confidence interval, 1·4 to 4·7), which is consistent with our relative risk of 3·3.[22] Jackson *et al* reported findings from 57 orchidopexies (68 testes).[23] Seven testes had associated hydrocoeles (10·3%), 51·5% had hernial sacs and 44·1% a patent processus vaginalis. The figure for hernial sac is similar to the 55·0% (55/100) in Scorer's series.[5] Heath *et al* reported a figure of only 21·2% (28/132).[24]

SEASONALITY

Two other studies have considered seasonality in cryptorchidism.[22 25] Hjertkvist *et al* found a peak in births of cryptorchid babies in February and March and a deficit later in the year, with the lowest odds ratio in November.[22] Jackson and Swerdlow found a peak in March and April.[25] In our series, however, the greatest peak occurred in September. The contrast between our results and those of Jackson and Swerdlow is surprising because their study was also carried out in Oxford district. Their method of ascertainment of cases was through orchidopexies carried out in Oxford district, so the birthplace of the children was not necessarily within it and children born in Oxford district might have had orchidopexies carried out elsewhere. It should be noted that both Hjertkvist *et al*[22] and Jackson and Swerdlow[25] identified their cases from orchidopexy lists. In our series some babies diagnosed with undescended testes may never have an orchidopexy but some with late descending testes may, by puberty, have had an orchidopexy. We found strong evidence for a cyclic pattern in the month of birth of babies with late descending testes with a major peak from November to January, and generally low rates during the summer months. It has been suggested that the testosterone surge at or just after the time of birth is necessary for testicular descent.[26] It might be postulated that the late descending testis lacks only this testosterone surge whereas the development of the truly undescended testis is already compromised. The possibility that fetal testosterone production varies seasonally warrants investigation.

CRYPTORCHIDISM RATES AND ORCHIDOPEXY RATES

A number of studies have suggested that orchidopexy rates are substantially higher than cryptorchidism rates. Campbell *et al* reported a cohort based hospital discharge rate in Scotland of 3·8% for babies born between 1961 and 1985,[14] and we estimated the cumulative orchidopexy rate for babies born in England and Wales between 1975 and 1979 at 2·9%.[4] This is substantially greater than the 1·57% reported here (including the 24 still being followed up regularly although an orchidopexy has not yet been performed). Cooper and Little in a study of six district general hospitals suggested that orchidopexies performed for cryptorchidism exceed the expected number by a factor of 4.[27] This may be an overstatement as they assumed a cryptorchidism rate of 1%.

One suggested explanation is the 'ascending testis' described by Atwell.[28] In an earlier paper[29] we reported that 40% of the first 45 babies with late descending testes included in this study were cryptorchid at one year, and that 24% of 17 babies with a hydrocoele but apparently normally descended testes at birth had undescended testes at one year.[30] We now report that 71 of the 187 late descenders examined at 3 months had undescended testes by our criteria. If all these were to have surgery, plus the 19 with cryptorchidism at 3 months still under review, plus the 85 cryptorchid at 3 months known to have had an orchidopexy, and the four with normal testes, the cumulative orchidopexy rate would be 2·4% ((71+19+85+4)/7400). It will only be by continuing to follow up this cohort of boys that their cumulative orchidopexy rate can be determined and related back to our findings at birth.

Report prepared by P E Ansell, D Bull, C E D Chilvers, C A C Coupland, and M C Pike.

This study would not have been possible without the help of all the mothers who allowed us to examine their babies, the midwives at the John Radcliffe Hospital, and the general practitioners of Oxfordshire. We thank Ruth Gell, Melanie Cumpston, Lisa Daniel, and Penny Kelham for manuscipt preparation. CACC is supported by a grant from the Cancer Research Campaign. The Institute of Cancer Research receives support from the Cancer Research Campaign and the Medical Research Council.

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Pertussis, pertussis, pertussis

Despite immunisation, pertussis, as we all know, is still around. Although the majority of those affected are infants and young children, data from the United States has shown an increase in the disease at older ages. The February issue of the *American Journal of Diseases of Children* contains four papers concerned with various aspects of pertussis.

A paper from Japan (Tatsuo Aoyama and colleagues, pages 163–6) concentrates on the disease in adults, its clinical features, and the importance of adults in the spread of the disease. The families of 89, presumably child, index cases were studied and 37 of 203 adults in these families had clinical pertussis. Of these 37 adults, 10 were the first case in the family (primary case), eight developed symptoms within a week of the primary case (co-primary), and 19 developed symptoms between one and four weeks after the primary case (secondary cases). In this study about 10% of adults exposed to the disease within a household developed the disease and about 16% of infants with the disease had been infected by an adult in the same household. About 10% of primary cases were adult.

Sixty eight asymptomatic adults had blood taken for serology and nasopharyngeal swabs for culture and 17 of them were shown to have 'subclinical' infection, although in fact eight of them had mild symptoms. The symptoms in the adults were different from those in the children. All patients had a protracted paroxysmal cough which was worse at night as that was a diagnostic criterion. Most (86%) of the adults complained of shortness of breath during a paroxysm and a tingling sensation in the throat but few (less than 10%) had either a whoop or vomiting with the cough. No adult became cyanosed during a coughing paroxysm.

The lymphocytosis seen in children did not occur in adults and nasopharyngeal swabs produced scantier growths of *Bordetella pertussis* than in children. The authors quote unpublished data indicating that the lymphocytosis of pertussis decreases with age in unimmunised patients and does not occur in those who develop the disease despite previous immunisation.

Papers from Sweden and the United States in the same issue confirm that adults are a large proportion of cases in recent outbreaks. Currently pertussis vaccine is not recommended above the age of 7 years as adverse effects are said to be more frequent at an older age. In the United States children are given two doses, at 15 months and between 4 and 6 years, in addition to the three doses in infancy given in Britain. Perhaps with the advent of acellular vaccines, and if further epidemological data confirms the importance of the disease in adults, it will be necessary to consider extending the immunisation schedule to later ages.

ARCHIVIST

Archives of Disease in Childhood 1992; **67**: 900–904

Birth weight and hospital admission before the age of 2 years

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Abstract

Admission rates to hospital of children born weighing 1500 g or less were compared with those born with birth weights over 1500 g in a retrospective analysis of routinely collected data from the Oxford Record Linkage Study. The children were born in the three five year periods 1968–72, 1974–8, and 1979–83 to women resident in Oxfordshire and West Berkshire. The main measures of the study were survival rates to 28 days after birth and hospital admissions of survivors up to the age of two years.

Among babies weighing 1500 g or less, neonatal survival rates rose from 350·2 per 1000 total births in 1968–72 to 577·4 per 1000 among births in 1979–83. Over the same period, the proportion of children admitted to hospital at least once before the age of 2 years rose from 213·6 per 1000 survivors to 444·4 per 1000. In the children with birth weights over 1500 g, survival rates rose from 985·5 to 995·9 per 1000 births and hospital admission rates rose from 98·2 to 144·4 per 1000 survivors over the same time period.

Although very low birthweight children did not contribute significantly to total hospital bed occupancy, because their numbers were small in relation to the total number of children in the population, their contribution increased between the five year periods 1968–72 and 1979–83. It should therefore be continuously monitored using routine systems.

Over the past 20 years, the survival rates of very immature babies have increased dramatically. As a result, many children who would have died in the past are now surviving and living healthy normal lives. Nevertheless, there has been speculation about the consequences of this increased survival in terms of overall levels of morbidity among the survivors. There is already evidence that the prevalence of cerebral palsy among low birthweight children is rising[1 2] and also of an increase in less dramatic forms of morbidity among these vulnerable babies.[3–5]

Ideally, routine child health surveillance systems should be able to provide the information that is required to monitor the evolving situation in the light of continuing increases in the survival rates. Unfortunately, despite considerable investment of resources in planning and piloting these systems in the UK, those in use in England are not yet able to generate the standard information that is required on a national basis.

Five years ago, we reported the results of an investigation which made use of the Oxford Record Linkage Study to examine trends in admission rates among very low birthweight and heavier children born in the two five year periods 1968–72 and 1974–8 in Oxfordshire and West Berkshire, to women living in those areas.[4] Our analysis demonstrated a rise in the absolute and relative risks of hospital admission among very low birthweight children. The increase in absolute risk was largely accounted for by increased admission rates of babies with respiratory infections, structural defects, such as hernia, trauma and poisoning, and miscellaneous other conditions. In this paper we report an extension of our earlier analysis to the children born during the period 1979–83, during which there was a further increase in survival rates among low birthweight babies.

Methods

A detailed account of our study methods has already been published.[4] The study used the Oxford Record Linkage Study to obtain routinely collected data.[6] The database includes records of all births, deaths, and hospital admissions occurring in Oxfordshire and West Berkshire. Records relating to *all* babies weighing 1500 g or less at birth, together with those for random samples of heavier babies, were extracted from the maternity file. The analysis was restricted to babies born to women who both lived and delivered in the study area during the five year periods 1968–72, 1974–8, and 1979–83. In each of these quinquennia, approximately 6% of births to residents of Oxfordshire and West Berkshire took place outside the study area. These were not included in the analyses. In addition, it was not possible to trace admissions of children to hospitals outside the Oxford region. Copies of death certificates were obtained for all children who died under the age of 2 years.

An episode of hospitalisation was defined as an inpatient stay or a day case admission occurring after the initial discharge from hospital after birth, and at any time between 28 days and 2 years. Data on hospital discharges were extracted manually from listings of records of all discharges of children admitted before the age of 2 years, by matching on names and dates of birth. The data extracted included age at admission, duration of stay, and the diagnoses recorded on discharge from hospital. The hospitalisation rate was calculated as the number of discharges per 1000 children surviving 28 days after live birth. The diagnoses recorded on discharge from hospital were grouped into 11 cate-

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Accepted 9 March 1992

Table 1 Changes between 1968–72 and 1979–83 in the numbers of deaths and mortality rates among babies born to women living and delivering in Oxfordshire or West Berkshire, by birth weight

	Birth weight of 1500 g or less				*Birth weight over 1500 g*			
	1968–72	*1974–8*	*1979–83*	*% Change in rate between 1968–72 and 1979–83*	*1968–72*	*1974–8*	*1979–83*	*% Change in rate between 1968–72 and 1979–83*
Total births	614	379	433		67863	52751	56039	
Live births	523	295	354		67393	52468	55894	
Stillbirths*	191 (311·1)	84 (221·6)	79 (182·4)	−41	470 (6·9)	283 (5·4)	145 (2·6)	−62
Early neonatal deaths†	199 (470·5)	99 (335·6)	86 (242·9)	−48	423 (6·3)	260 (5·0)	169 (3·0)	−52
Late neonatal deaths†	9 (21·2)	15 (50·5)	18 (50·8)	+140	90 (1·3)	76 (1·4)	60 (1·1)	−15
Postneonatal deaths†	8 (18·9)	12 (40·6)	4 (11·3)	−40	327 (4·9)	217 (4·1)	218 (3·9)	−20
Deaths 366–729 days†	0 (0·0)	1 (3·4)	1 (2·8)		72 (1·1)	40 (0·8)	23 (0·4)	−64
Live born babies surviving to 28 days†	215 (350·2)	181 (477·6)	250 (577·4)	+65	66880 (985·5)	52132 (988·3)	55665 (995·9)	+1

*Rates per 1000 total births shown in parentheses.
†Rates per 1000 live births shown in parentheses

gories based on codes from the eighth and ninth revision of the *International Classification of Diseases.*[7 8] As up to four diagnostic codes could be recorded for each episode, rates were based on the number of times a diagnostic grouping was mentioned.

It is possible that there were changes over time in the predisposition among paediatricians to admit children to hospital, their use of diagnostic labels, and the way that these were recorded. In an attempt to control for this, the admission rates of the very low birthweight babies were compared with those of the samples of bigger babies by estimating the odds ratios and their 95% confidence intervals.[9]

Results

CHILDREN BORN WEIGHING 1500 G OR LESS

Table 1 shows that the chance that a baby born weighing 1500 g or less in the years 1979–83 was 65% more likely to survive until the end of the neonatal period than a baby born in the period 1968–72. In contrast, table 2 shows that over the same period the rate of admission to hospital before the age of 2 years doubled, from 218·6 to 444·4 per 1000 survivors. As noted in our earlier paper the increased rate of admission between 1968–72 and 1974–8 was accounted for by an increase in the rate of admission of babies with infections, structural defects, trauma and poisoning, and miscellaneous 'other' conditions, among which, asthma predominated.[4] Table 3 shows that, with the exception of structural defects other than hernias, the same categories, and in particular infections and miscellaneous other conditions, contributed to the more substantial rise between 1974–8 and 1979–83 in the overall rate of hospitalisation. In addition, there were statistically significant rises in the admission rates for nutritional disorders, convulsions, and 'perinatal' conditions, which included bronchopulmonary dysplasia, the sequelae of necrotising enterocolitis, and haemolytic disease.

CHILDREN BORN WEIGHING MORE THAN 1500 G

Table 1 shows that between 1968–72 and 1979–83, there was a 1% increase in survival to 28 days after live birth among children born weighing over 1500 g. The overall rate of hospitalisation among such children born in the period 1974–8, shown in table 2, was somewhat lower than for similar children born during 1968–72. This change was largely explained by reduced rates of admission for congenital malformations, structural defects and other anomalies, and convulsions, shown in table 3. For children born from 1979–83, however, the overall rate of hospitalisation was 143·3 per 1000 survivors, substantially higher than the rate of 89·4 for children born in the period 1974–8. This rise reflected increases in all but two of the diagnostic categories, but was mainly seen in increased mentions of diagnoses of infections, malformations, convulsions, perinatal and other conditions, notably non-specific symptoms and signs.

Table 2 Numbers and rates of readmission by period of birth and by birth weight

	Birth weight of 1500 g or less			*Sample of children with birth weight over 1500 g*			*Odds ratios associated with being very low birth weight (95% confidence interval)*		
	1968–72	*1974–8*	*1979–83*	*1968–72*	*1974–8*	*1979–83*	*1968–72*	*1974–8*	*1979–83*
Total births	614	379	433	1202	742	924			
No of liveborn babies surviving up to 28 days*	215 (350·2)	181 (477·6)	250 (577·4)	1181 (982·5)	738 (994·6)	921 (998·7)	0·0096 (0·0060 to 0·0152)	0·0090 (0·0018 to 0·0135)	0·0044 (0·0014 to 0·0140)
No of children rehospitalised†									
Once	47 (218·6)	49 (270·7)	111 (444·4)	116 (98·2)	66 (89·4)	132 (143·3)	2·57 (1·76 to 3·74)	3·78 (2·50 to 5·72)	4·77 (3·50 to 6·51)
Twice	21 (97·7)	12 (66·3)	34 (136·0)	20 (16·9)	12 (26·3)	23 (25·0)	6·28 (3·34 to 11·8)	4·30 (1·90 to 9·73)	6·15 (3·55 to 10·6)
Three or more times	12 (55·8)	12 (66·3)	24 (96·0)	5 (4·2)	2 (2·7)	7 (7·6)	13·3 (4·62 to 38·0)	26·1 (5·79 to 11·8)	13·87 (5·9 to 32·59)

*Rate per 1000 live births shown in parentheses.
†Rate per 1000 babies surviving to 28 days shown in parentheses

COMPARISONS BETWEEN TRENDS FOR CHILDREN WITH VERY LOW AND HIGHER BIRTH WEIGHTS

Table 4 shows that the overall odds ratio for rehospitalisation among low birthweight children compared with those born with higher birth weights rose from 2·57 for those born in 1968–72 to 3·78 for those born in 1974–8 and 4·77 for those born in 1979–83. Among births in 1979–83, the diagnostic categories for which the odds ratios were highest, were structural defects and other anomalies, hernia, perinatal conditions, nutritional deficiency/disorders, and chest infections. Only in the case of nutritional and deficiency disorders was there a greatly increased risk of admission in 1979–83 compared with 1974–8 but this was still no greater than would be expected by chance. Within this category the most common diagnoses were 'failure to thrive' and 'feeding problems'.

Table 3 Numbers of mentions of diagnostic categories on discharge records by birth weight (rates per 1000 survivors)

	Birth weight of 1500 g or less			*Birth weight over 1500 g*		
	1968–72	*1974–8*	*1979–83*	*1968–72*	*1974–8*	*1979–83*
Neonatal survivors	215	181	250	1181	738	921
No of children readmitted at least once	47	49	111	116	66	132
Diagnostic category						
Malformation	20	12	21	21	7	31
	(93·0)	(66·3)	(84·0)	(17·8)	(9·5)	(33·7)
All structural defects	17	23	29	19	5	10
	(79·1)	(127·1)	(116·0)	(16·1)	(6·8)	(10·9)
Hernia	14	18	27	13	2	6
	(65·1)	(99·4)	(108·0)	(11·0)	(2·7)	(6·5)
Other anomalies	9	5	12	11	1	4
	(41·9)	(27·6)	(48·0)	(9·3)	(1·4)	(4·3)
All infections	21	28	98	41	29	89
	(97·6)	(154·6)	(392·0)	(34·7)	(39·3)	(96·6)
Upper respiratory infection	1	4	7	3	1	4
	(4·7)	(22·1)	(28·0)	(2·5)	(1·3)	(4·3)
Chest infection	7	12	37	15	9	17
	(32·6)	(66·2)	(148·0)	(12·7)	(12·2)	(18·5)
Trauma/poisoning	2	4	10	32	21	24
	(9·3)	(22·1)	(40·0)	(27·1)	(28·5)	(26·1)
Nutritional deficiency/disorders	10	6	30	4	8	6
	(46·5)	(33·1)	(120·0)	(3·4)	(10·8)	(6·5)
Convulsions	5	3	14	11	3	19
	(23·3)	(16·6)	(56·0)	(9·3)	(4·1)	(20·6)
Perinatal conditions	4	2	27	2	1	8
	(18·6)	(11·0)	(108·0)	(1·7)	(1·4)	(8·7)
Other/or not known	15	21	64	22	14	35
	(69·8)	(116·0)	(256·0)	(18·6)	(19·0)	(38·0)

Table 4 Odds ratios and 95% confidence intervals of readmission for very low birthweight children compared with heavier children for each diagnostic category

	Year of birth		
	1968–72	*1974–8*	*1979–83*
For all children admitted	2·57	3·78	4·77
	(1·76 to 3·74)	(2·50 to 5·72)	(3·50 to 6·51)
For children admitted with:			
Congenital malformation	5·67	7·42	2·63
	(3·01 to 10·65)	(2·8 to 19·12)	(1·48 to 4·67)
Structural defects	5·25	21·34	11·95
	(2·68 to 10·28)	(7·99 to 56·99)	(5·74 to 24·90)
Hernia	6·25	40·62	18·46
	(2·90 to 13·51)	(9·34 to 176·87)	(7·53 to 45·26)
Other anomalies	4·65	20·94	11·56
	(1·90 to 11·35)	(2·43 to 180·35)	(3·69 to 36·16)
All infections	2·29	4·47	6·03
	(1·74 to 5·20)	(2·59 to 7·74)	(4·31 to 8·43)
Upper respiratory infection	1·83	16·66	6·60
	(0·19 to 17·22)	(1·85 to 149·93)	(1·92 to 22·74)
Chest infection	2·62	5·75	9·24
	(1·54 to 6·49)	(2·34 to 13·87)	(5·10 to 16·72)
Trauma/poisoning	0·34	0·77	1·56
	(0·08 to 1·42)	(0·26 to 2·28)	(0·73 to 3·30)
Nutritional deficiency/disorders	14·35	3·13	20·80
	(4·46 to 46·20)	(1·07 to 9·13)	(8·55 to 50·58)
Convulsions	2·53	4·15	2·82
	(0·87 to 7·36)	(0·83 to 20·74)	(1·39 to 5·70)
Perinatal conditions	11·18	8·23	13·82
	(2·03 to 61·40)	(0·74 to 91·32)	(6·19 to 30·83)
Other	3·95	6·79	8·71
	(2·02 to 7·75)	(3·38 to 13·64)	(5·60 to 13·54)

Table 5 Changes over time in the number of episodes and length of stay by birth weight

	Year of birth		
	1968–72	*1974–8*	*1979–83*
Average No of episodes/child			
≤1500 g	1·8	1·8	1·9
>1500 g	1·2	1·2	1·2
Median length of stay/episode (days)			
≤1500 g	4·8	3·5	4·2
>1500 g	3·6	2·8	2·1
Median length of stay/child (days)			
≤1500 g	7·6	4·9	6·1
>1500 g	4·5	3·1	2·3

Table 6 The contribution of very low birthweight children to total hospital inpatient stays by children aged between 28 days and 2 years

	Year of birth		
	1968–72	*1974–8*	*1979–83*
Birth weight 1500 g or less as:			
% Of all children admitted	0·9	1·0	1·4
% Of all admission episodes	0·7	1·0	2·0
% Of all days spent in hospital	1·5	1·9	4·4

For children born weighing 1500 g or less, table 5 shows no clear trends over time in the average number of episodes of rehospitalisation per survivor, or in the median length of stay, whether expressed per episode or per child. Among the children with higher birth weights, the average number of episodes of hospitalisation remained constant at 1·2 over the whole of the period studied. In contrast to the lack of any clear trend among children with very low birth weights, the median length of stay, per episode and per child, fell progressively. As a consequence of this, the contribution of children with very low birth weights to the overall numbers of inpatient stays has increased over the three periods as table 6 shows.

Discussion

Our results confirm that surviving very low birthweight babies are a vulnerable group of children who experience substantially higher levels of subsequent hospitalisation than heavier babies. Others have reported readmission rates of between 32 and 53% in the first year of life[3 10 14] against a background of admission rates of between 10 and 15% for all children.[14 15] Our findings are consistent with this range.

Between the five year periods 1968–72 and 1979–83 the rate of hospitalisation of very low birthweight babies who survived the first 28 days of life doubled, while their neonatal mortality fell by 65%. The rate of hospital admission among heavier survivors fell between the first two cohorts, but then rose in the cohort born in 1979–83. This latter finding is consistent with the results of a cross sectional study covering a much larger proportion of the population of the Oxford region but restricted to the two years 1975 and 1985.[16] That study reported an increase in admissions of all children aged 0–14 years. This was mainly accounted for by a rise in admissions to *medical* as opposed to surgical specialities.

The contribution of very low birthweight babies to the total use of hospital beds by children between the ages of 28 days and two years is small, as table 6 shows. It is increasing, however, and there is a possibility that this increased bed use may also continue beyond the second year of life. In 1979–83, 34% of the lighter babies were readmitted in the first year of life, compared with 9% of the heavier babies. In the second year of life, 10% of the smaller children but only 5% of the heavier group were readmitted for the first time. Data from the 1946 national cohort suggested that the higher rate of admission for very small babies did not persist after the second year of life.[17] More recent data from the Scottish low birthweight study (L Mutch, in preparation) shows a continued high rate of hospital admission between 2 and 4·5 years of age. By the age of 2 years, 23% of children who weighed under 1500 g at birth had been readmitted, but by 4·5 years this figure had reached 65%.

The contribution of children born weighing under 1500 g to all hospital admissions rose by 1·5 times from 0·9% in 1968–72 to 1·4% in 1979–83. This increase was lower than the 2·9-fold rise in their contribution to the total number of days spent in hospital.

There are several possible explanations for the increased rates of readmission among the cohorts of children born during the early 1980s. It has been suggested that the increase in the rate of hospital admission may reflect greater pressure from parents or general practitioners for inpatient care, or 'lower thresholds for admission resulting, in part, from the increased availability of beds because of the diminishing lengths of stay'.[16] Although our study was designed to take account of changes in the threshold for admission within each of the paired cohorts, the data do not allow us to investigate changes in the threshold over time. It seems to us that this issue could only be addressed in studies that explore reasons for the decision to refer a child to hospital, and the admitting doctor's decision to admit the child. This cannot be ascertained retrospectively from routinely collected data.

Another possible contribution to the trends might be that doctors are referring and admitting to hospital children suffering from conditions that were not previously thought to be amenable to treatment. This notion does not receive support from the observed pattern of diagnostic categories, among which infections of the upper and lower respiratory tract dominated.

Lastly, the rising readmission rates may partly reflect a real increase in the prevalence of illness in these children. Even if this is so, it seems unlikely that child health has deteriorated to the extent implied by the rise in hospitalisation rates, particularly among the heavier group of children. As far as the very low birthweight children are concerned, however, this increase would be consistent with trends seen in other relevant data. Although the increasing survival of very low birthweight babies has been accompanied by an increase in the number of neurologically intact children in the population, the number of these children who have cerebral palsy has also been increasing.[18] Furthermore it has been reported that the chances of readmission are likely to be higher among children with a handicapping condition.[14]

Our analyses are set against the background of increased rates of admission for all age groups in the Oxford region[19] and the debate about how these should be interpreted. For all children, it has been shown that although the number of admissions has increased, the total time spent in hospital has decreased.[20] Table 5 shows that whereas this is true for the heavier children in our study, there is no clear trend for the very low birthweight children.

Like ours, the studies of all admissions were based on data collected routinely and brought together as part of the Oxford Record Linkage Study. In theory, population based district information systems which district health authorities have been told to implement by April 1 1993[21] should be able to provide similar information. Meanwhile, it has been shown that linkage of routine Körner data about successive hospital admissions is technically feasible,[22 23] although use of readmission rates as an outcome measure of hospital inpatient care has been challenged.[24] Linkage between maternity data and subsequent hospital admission of babies poses an added problem, however, as does the incompleteness of Körner maternity data,[25] but the importance of overcoming these difficulties cannot be overemphasised.

CONCLUSIONS

Although very low birthweight children did not contribute significantly to total hospital bed occupancy because their numbers were small in relation to the total number of children in the population, their contribution increased between the five year periods 1968–72 and 1979–83. Future patterns should therefore be monitored continuously using routine systems.

We should like to thank Myfanwy Griffiths, Margaret Godden, and Tony Peeke at the Oxford Record Linkage Study who kindly provided the raw data, and Dr Michael Goldacre, the director, for access. Colleagues at the National Perinatal Epidemiology Unit have commented on successive drafts and have, as always, given helpful advice. Colin Pritchard of the Public Health Research Unit gave useful advice on a later draft. Grateful thanks are due to Gaye Bell, Pam Hughes, Lyn Pilcher, and Caroline Caldicott for help in preparing the manuscript.

Lesley Mutch was supported by a project grant from the Department of Health and Social Security, as it then was. The National Perinatal Epidemiology Unit is funded by the Department of Health, as are Myfanwy Griffiths and Margaret Godden.

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Pertussis (2): acellular vaccines and household contact

'Oh, come on', I said. 'How can they do it?' I said. 'What parents are going to agree to it? You can't conduct a placebo controlled trial of pertussis vaccine. Well, can you?' Yes, you can; and the reason why is mentioned as a casual passing comment, after five columns of print, by Jan Storsaeter and colleagues (*American Journal of Diseases of Children* 1992;**146**:167–72). Routine pertussis immunisation was stopped in Sweden in 1979 so no child in the trial was denied something the rest of the population was getting. If only they'd said that in their introduction they could have saved me a lot of adrenaline.

Nearly 4000 children aged 6 to 11 months were included in the trial. In each group of eight children three were given a two component Japanese acellular pertussis vaccine (JNIH-6), three were given a monocomponent acellular vaccine (JNIH-7), and two were given placebo injections. Each child received two injections two months apart. Previous studies using whole cell vaccines have shown rates of protection after household contact of 50 to 60% in Britain and 70–90% in the United States, the higher protection in the United States being possibly a consequence of the extended five dose course used there.

On follow up for at least 14 months after the second injection those who received placebo were more likely than those who were given a vaccine to suffer from pertussis. For the JNIH-6 vaccine the difference was highly significant ($p<0{\cdot}001$) but for the JNIH-7 vaccine it was less so ($p=0{\cdot}09$). After househould contact culture confirmed pertussis occurred in 13 of 16 (81%) in the placebo group, seven of 26 (27%) in the JNIH-7 groups, and 10 of 19 (53%) in the JNIH-6 group.

The estimated vaccine efficacy after household exposure for culture confirmed pertussis was 35% for the JNIH-6 vaccine and 67% for the JNIH-7. For clinical pertussis with 21 days or more of paroxysmal cough the estimated efficacies were 58 and 82% respectively. These differences did not reach statistical significance.

Blood samples for serological tests were obtained from children and adults after household exposure but no association was found between serum concentrations of antibodies against pertussis toxin or filamentous haemagglutin and the degree of protection. The authors conclude that the two component JNIH-6 vaccine is more protective against community exposure but there is no significant difference between the vaccines as regards protection after household exposure.

ARCHIVIST

Suspected child abuse: cost in medical time and finance

C L Summers, E M Molyneux

Abstract

In a prospective study the number of children attending the Royal Liverpool Children's Hospital (RLCH) for examination after allegations of child abuse, and the type of abuse involved, was recorded from July to December 1990. The cost to the hospital of these examinations and initial investigations was assessed. The study was carried out in the major and minor accident and emergency departments and the Rainbow Centre of the RLCH. In six months 181 children were examined. Cases of sexual abuse and non-accidental injury were seen in equal numbers. Girls outnumbered boys and 60% were referred by social services. The costs over the six month period were £31 739. The minimum projected annual cost is £63 500. We conclude that the cost of running an effective service for the initial assessment of children who are possible victims of child abuse is considerable in practical terms and in medical time.

There have been many studies of the physical and emotional consequences of child abuse,[1–4] but little attention has been given to the financial cost of child abuse for the health service and, in turn, for society. The cost in medical time is considerable but has not been documented. This study was undertaken as an audit of the problem of child abuse at the Royal Liverpool Children's Hospital (RLCH). We monitored all patients seen with suspected child abuse over a six month period, and assessed the financial implications for the hospital.

The policy for managing child abuse in Liverpool has been written at the direction of, and approved by, the Area Child Protection Committee (ACPC). It is contained in a child protection manual. This policy follows the guidelines recommended by such documents as *Working Together*.[5] It is followed by all the agencies involved in the diagnosis and management of children suspected of child abuse and emphasises the multidisciplinary approach to such children. If an allegation of non-accidental injury comes to social services a social worker, through a senior child protection consultant, investigates the allegation. She may liaise with her counterpart in the police force. One or other of these agencies will contact a paediatrician experienced in child abuse work to examine the child. In cases of non-accidental injury where a criminal investigation is likely to take place, the police may request that a police surgeon (usually a local general practitioner) be present at the examination with the paediatrician. Equally, the paediatrician may request that a police surgeon attend for such a case. In cases of suspected child sexual abuse a social worker and a designated member of the police force, who are both members of the child protection team, together review the allegation, interview the child, and ask for a joint examination of the child by a police surgeon and a paediatrician. In most cases of non-accidental injury where the alleged perpetrator is a member of the family, siblings are examined for evidence of injury. In cases of suspected child sexual abuse the siblings are examined if there is any suspicion of their involvement. If they are involved they become index cases.

Teachers, general practitioners, and other professional carers for a child are advised to contact social services immediately they suspect a child of child abuse. If the injuries are severe they are asked to bring the child directly to hospital to see a paediatrician.

At hospital, when a child is seen or admitted for another cause, but child abuse is suspected, there are clear guidelines for staff to notify the consultant in charge and the hospital social workers.

The doctors who examine children for child sexual abuse are paediatricians. The senior staff in the accident and emergency department are two experienced paediatrically trained consultants who have attended training sessions in forensic medicine, and one clinical assistant with over 20 years experience in this field. Both consultants in the accident and emergency department are members of the ACPC of either Liverpool or South Sefton. All three doctors have considerable experience in the problem of child abuse. Medical paediatric registrars, under the supervision of their own consultants, see children suspected of non-accidental injury.

Children who fail to thrive are investigated by paediatricians. Emotionally abused children are referred to a mental health team comprising psychologists, psychiatrists, and psychiatric social workers.

In June 1990 a centre for the examination of suspected cases of child abuse was opened in the RLCH, at Alder Hey, Liverpool. The centre is adjacent to the accident and emergency department and consists of a reception room, office, three interview rooms—one equipped with a video recording system—and an examination room with bathroom attached. The unit is known as the Rainbow Centre and is staffed by a full time administrator, a part time secretary, and a staff grade nurse who works both in the centre and in the accident and emergency department.

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Accepted 15 February 1992

When it was first opened the Rainbow Centre was used solely for suspected sexual abuse, while physically abused children were seen in the accident and emergency department. Since February 1991 all children suspected of child abuse have been seen in the centre.

The accident and emergency unit of the RLCH is on two sites. The major unit is at Alder Hey and gives a 24 hour service with the full back-up facilities of a paediatric hospital: 53 000 new patients were seen in 1990. The inner city department is a minor casualty service open daily from 9 am to 10 pm: 12 000 new patients attended in 1990. The two accident and emergency departments and the Rainbow Centre receive children from Liverpool, South Sefton, St Helens, and Knowsley and even further afield. The total population of children under 16 years of age in these areas is 227 954. Not all injured or abused children from this area are seen in the RLCH: staff in other hospitals and police stations within the area also see and diagnose child abuse.

Table 1 Type of suspected child abuse

	Child sexual abuse	*Non-accidental injury*	*Child sexual abuse/ non-accidental injury*	*Neglect*	*Siblings*	*Total*
Boys	17	32	1	0	26	76
Girls	52	36	2	1	14	105
Total	69	68	3	1	40[1]	181

[1] Of all siblings examined, 34 for non-accidental injury, four child sexual abuse, and two child sexual abuse/non-accidental injury.

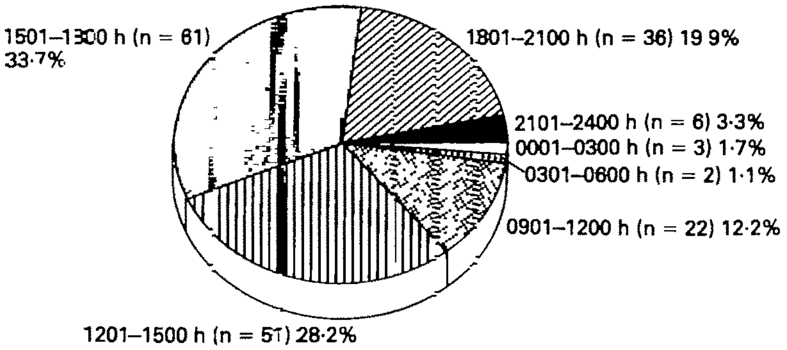

Figure 1 Time of examination in child abuse (n=181).

Table 2 Age and reason for referral (n=181)

Age (years)	*Child sexual abuse*	*Non-accidental injury*	*Child sexual abuse/ non-accidental injury*	*Neglect*	*Siblings*	*Total*
0–1	0	5	0	1	4	10
>1–4	31	27	1	0	21	80
5–9	19	20	2	0	13	54
10–14	15	12	0	0	2	29
15/16	4	4	0	0	0	8

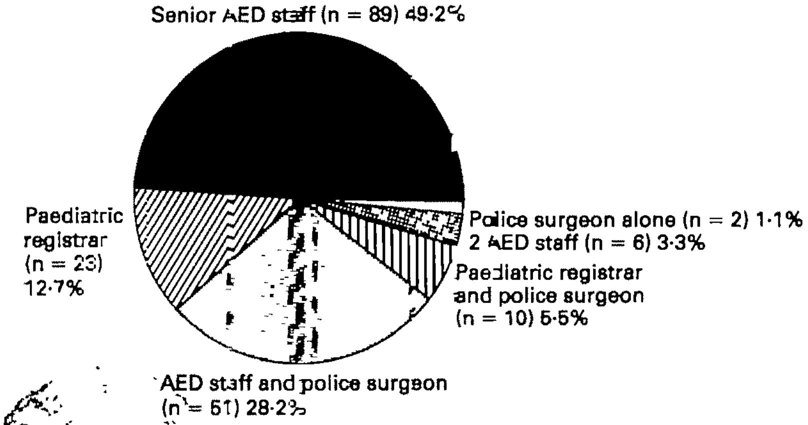

Figure 2 Medical examiners in child abuse (n=181). AED=accident and emergency department.

Methods

From 1 July to 31 December 1990 a proforma was completed by the examining doctor for all cases of suspected child abuse. Information recorded included the age and sex of the child, the reason for referral and by whom referred, the date and time of examination and its findings, any investigations performed, and where the child went after leaving the hospital. For a 13 week period, 7 July 1990 to 18 October 1990, details included the time it took for an examination to be carried out.

Results

During the six month study period 181 children were examined for possible child abuse (table 1). There were 105 (58%) girls and 76 (42%) boys. Table 1 shows the sex of the children and the reasons for their examinations. Of the 181 children, 107 (60%) were referred to the hospital by social services, 41 (22%) by the police, and 12 (6%) by general practitioners. Ten (5%) were brought directly by parents, and three (2%) by other relatives. Seven (4%) were referred to the accident and emergency department by other hospital staff. One child was self referred and one was sent to the unit by the National Society for Prevention of Cruelty to Children (NSPCC). Altogether 153 (85%) of the children were accompanied to the hospital by a parent, four came with another relative, and 24 were brought by an adult other than a parent or relative; this was usually a social worker.

The distribution of attendances by month was fairly constant with peaks in July and September (41/month compared with 23/month in October to December). Children were seen evenly throughout the week from Monday to Friday (mean 1·5 patients per day) but fewer presented at weekends (0·6 per day). The time of day of examinations is shown in fig 1, and the ages of the children and the indication for the examination in table 2.

Fifty eight children were seen in the inner city minor casualty department, 76 in the Rainbow Centre, and 47 at Alder Hey accident and emergency department. The examinations were carried out by senior accident and emergency staff, police surgeons, and medical paediatric registrars. Figure 2 shows the number of children examined by members of each group of practitioners.

The average time taken to examine a child suspected of child sexual abuse was 50 minutes (range 20–235 minutes) and for non-accidental injury was 59 minutes (range 15–220 minutes).

In possible cases of non-accidental injury the examination confirmed the suspicions in 54% of cases (table 3). In child sexual abuse 13% had clear physical findings of the abuse. A number of other physical findings came to light: some of these were suggestive of child sexual abuse; some had been confused with non-accidental injury (table 4). No sibling who was examined was found to have suffered child abuse.

The majority of children (71%) required no investigation beyond a careful examination. Others required a variety of investigations (table 5). Altogether 136 (75%) children went home after being examined, 13 (7%) were admitted, 10 (5·5%) were subject to a place of safety order, nine (5%) went into social services care, and nine (5%) went into foster care. Two children went home with a relative and one child went home with a friend. One child aged 2·5 years who had multiple injuries including a fractured skull and ruptured liver was dead on arrival in minor casualty.

THE COST OF CHILD ABUSE EXAMINATIONS

The Rainbow Centre carries the annual salary costs of the part time clerk-typist (£4558·38), the administrator (£13 515), a staff nurse (£13 164), and seven senior casualty sessions/week (£20 062). Incidental expenses run to £550/year. During the six month study period additional medical time cost £3680. Investigations totalled £2132·85 in the six month period. The hospital 'hotel' bill for 64 nights at £180/day was £11 520. These costs total £31 738·53 over the study period giving an estimated annual cost to the Rainbow Centre and hospital of £63 500.

Table 3 Results of examination in child abuse (n=181)

	Child sexual abuse	*Non-accidental injury*	*Child sexual abuse/ non-accidental injury*	*Neglect*	*Siblings*	*Total*
Diagnosis confirmed	9	38	1	0	0	48
Not confirmed	60	30	2	1	40	133

Table 4 Other physical findings

Miscellaneous diagnoses in non-accidental injury	Flea bites (n=1) Birthmark (n=1) Henoch-Schonlein purpura (n=1)
Miscellaneous diagnoses in child sexual abuse (Some of these fingings would corroborate a diagnosis of child sexual abuse but not be conclusive evidence for the diagnoses)	Threadworms (n=4) Redness of perineum (n=4) Vulvovaginitis (n=4), one with introitus at upper limit of normal for age Labial adhesions (n=2) Adhesions of fourchette (n=2) Candida (n=1) Vaginal discharge (n=1) Ovarian cyst (n=1) Lichen sclerosis et atrophica (n=1) Bruised inner thigh (n=1) Slight vestibular swelling (n=1) Clear history of fingering (n=1) Anal dilatation due to constipation (n=1) Vaginal bruising consistent with accidental injury (n=1) Pubic hairs present, different from child's (n=1) Child appeared 'knowing' in examination (n=1)

Table 5 The investigations and their cost in child abuse

Investigation	*No*	*Cost*
None	129	
Radiograph of injured site	20	£400
Skeletal survey	21	£1050
Photography	23	£276
Full blood count and clotting studies	27	£356·40
Analysis of midstream specimen of urine	11	£44
Swabs	1	£6 45
Full forensic investigation	2	
		Total=£2132 85

A number of investigations were carried out 'out of hours' and this increased their cost considerably.

REASON FOR REFERRAL

In cases of non-accidental injury an injury may have been noted to have inadequate accidental explanation or an admission of intentional injury made. Many parents of children who were on the child protection register brought the attention of social workers to all the injuries of their children. An examination of the child was usually arranged at the hospital. This practise, and the routine examination of all siblings, led to many examinations failing to confirm non-accidental injury. In suspected cases of child sexual abuse 29 (42%) were investigated after comments made by the children themselves; 45% of these children were under 5 years of age. Twelve were seen because of concern about their behaviour, 12 due to concern for their siblings and indirectly for the children themselves. Eight girls were complaining of perineal soreness. Seven children were examined after a parent had made allegations of possible child sexual abuse to the child; four were due to continuing concerns regarding the family, and one was referred from another district for a second opinion before a court case.

Discussion

INCIDENCE

In England and Wales four children die as a result of child abuse each week and 40 000 children are on the child protection register.[5] During the six month period of this study, 181 children with alleged child abuse were seen in an urban paediatric hospital. The corresponding figure for July–December 1987 was 106 (1987 was chosen for comparison as the year predates the Cleveland inquiry that highlighted the problems of child abuse, and child sexual abuse in particular, in our society).

Several studies have noted an increase in allegations of child abuse in recent years. Meadow states that there has been an increase in child abuse of 4 to 5-fold over the last decade.[5] The NSPCC has collected annual figures for many years and reported that from 1983–7 (pre-Cleveland) there was an increase in reported child sexual abuse from 0·08–0·65/1000 children/year.[6]

In our study the referrals for child sexual abuse equal those for non-accidental injury. This probably reflects the frequency with which child sexual abuse is referred to the hospital. Other forms of child abuse may be dealt with in greater numbers by local agencies. Girls outnumber boys in child sexual abuse (68:44) in line with the national trend. In our study they outnumbered boys in non-accidental injury by 37 to 32.

COLLABORATION BETWEEN SERVICES

Most of the children (60%) were referred by social services. This reflects the policy of involving social workers at an early stage in allegations of child abuse. The police referred 22% of cases. These referrals, usually for child sexual abuse, were made after consultation between police and social workers and involved an examination carried out jointly by a paediatrician and police surgeon.

COST IN TIME

Altogether 94% of the children were seen between the hours of 9 am and 9 pm; 75% were seen between 9 am and 6 pm. Most of the examinations were carried out with prior arrangement so that children would not have to wait to be seen and investigations by the social services could be completed. Every effort was made not to examine children late in the evening, but sometimes distraught parents were insistent that their child be examined without any delay. Sometimes social services and police found it difficult to complete their investigations until the family were returned home from work or school.

Senior staff in the accident and emergency department saw 81% of the children which took 206 hours of clinical time, not accounting for time taken in writing reports, attending case conferences, and court appearances. This time commitment by medical staff needs to be taken into account when staffing levels in such a department are reviewed.

FINANCIAL COST

To provide a separate location for assessing victims of possible child abuse inevitably involves expense. The Rainbow Centre is a purpose designed area which fulfils the Department of Health guidelines of interagency cooperation in child abuse cases[7] in aiming 'to provide a sympathetic and peaceful atmosphere where the children can be examined and where their problems can be discussed with the police and social workers and doctors'.[8] Bamford and Roberts state that examinations for child sexual abuse 'should be conducted in absolute privacy in an environment where the child can be comfortable.'[9] The centre allows for a single joint examination by relevant staff in a room suitably equipped for all types of examination, 'so that the number of examinations to which a child is subjected is kept to a minimum'.[10] Although 70% of cases needed no further investigations, tests carried out on the other children were expensive (total £2133). The tests requested out of hours increased the cost of each request threefold

The minimum annual costs to this hospital of £63 500 take no account of capital costs to provide the centre and its maintenance. Further uncosted expenses include attendance at case conferences, court appearances, and the time taken in preparing reports for these. The police incur the costs of forensic examinations and of attendance of the police surgeon at examinations. The costs to the hospital have not included any medical treatments required by the children. The cost of follow up with counselling and other support has not been estimated.

CONCLUSION

The diagnosis and investigation of child abuse is a difficult and important area of paediatrics. It is expensive, not only in financial terms but also in time. This work is done by experienced staff; in the RLCH 82% of child abuse work in the six month study period was done by senior casualty staff. To ease this burden on two or three members of staff the suspected cases of non-accidental injury are now seen by paediatric medical registrars under the supervision of their paediatric consultant. Child abuse is demanding in time and energy of staff of the welfare agencies and in particular the social services. It is important to develop and maintain a multidisciplinary approach in a suitable setting such as the Rainbow Centre, but the financial and time commitment by medical staff and their institutions needs to be acknowledged and given support.

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Commentary

Child protection work is difficult to cost as the task is a multiagency one. The medical time involved is only one part of the overall expense. Summers and Molyneux have audited the cost of medical examination in units in their hospital. During the six month study period a diagnosis of abuse was confirmed in 48 out of 181 referred children. For a catchment area of total child population 227 954 this seems a low figure given that Liverpool has areas of severe urban deprivation. The absence of cases of neglect diagnosed during this period is surprising and reminiscent of figures produced for Glasgow in the 1980s.[1]

There is apparently a low level of confirmation of diagnosis, especially in the suspected sexual abuse cases (26·5% of total referrals, 13% of sexual abuse referrals confirmed). However it is not clear what model of diagnosis is being used or what happened to the 60 children referred with suspicions of sexual abuse where the diagnosis was 'not confirmed'.

The question has to be asked whether the social services and police in Liverpool are poor in their selection of cases referred, or whether doctors are over cautious in diagnosis. In Leeds in 1989 there were 823 referrals to paediatricians for suspected abuse or neglect. This included 475 children with suspected sexual abuse in which a definite or probable diagnosis was made in 237 children.[2]

Joint medical examination by a paediatrician and police surgeon was introduced at the time of Cleveland. The method has never been properly evaluated but is used in Liverpool (and some other centres) for sexual abuse cases and oddly in some cases of physical abuse (non-accidental injury) where criminal investigations are likely to proceed. Many cases of non-accidental injury were seen by paediatricians alone, the examination took on average a little longer than a joint examination, and a positive diagnosis was substantially more likely. It cost the tax payer less, as there was only one doctor to pay. It must be time to assess the joint examination as it may be an ineffective (in terms of diagnostic accuracy), expensive, and sometimes inconvenient practice (25% of examinations were performed after 6 pm, but it is unknown how many were joint). Whatever the reason, sexual abuse diagnosis in Liverpool as judged by these data has yet to get off the ground.

Although comparisons are always difficult, recent incidence studies in the USA suggest that approximately 1% of American children will experience some form of sexual abuse each year.[3] That sort of incidence would give Liverpool or Leeds 2000 cases per year. Obviously child protection starts with the family, the community, and school. Doctors often come at the end of a line of other professionals who may respond to the child's difficulties.

Summers and Molyneux remind us that protecting children is costly, but with the numbers seen are they getting good value from the staff of the Rainbow Centre? Referral has increased rapidly in recent times, but much unmet need remains and to what level we do not know. There has not been the increase in staffing medically which this expansion deserves. The authors have shown that above all the work takes time. Paediatric middle grade staff can be used to absorb some of this work but they need training, supervision, and support from consultants if the work is to be done well.

In addition to the initial medical examination and investigation, medical time is spent in case conferences, attending court, in follow up (it is not clear how this is done in Liverpool), re-examination, and treatment (psychological/physical).

Recently there have been attempts to put a price tag on the consequences of child abuse for society, again in the USA. With increasing evidence of the long term consequences accumulating, it seem likely that this will amount to very much more than our current expenditure on intervention.[4] As the expenditure increases it will become important that outcome measures to assess the results of strategies for prevention or intervention are developed and applied.

The arguments for and against special centres will continue. As 'there are few areas of paediatrics that have so rapidly expanded in clinical importance in recent years as the sexual abuse of children'[5] it is important that all paediatricians are trained, willing, and able to diagnose this as well as other types of abuse. The danger of the special centre is that the problem is seen as someone else's, in 'the unit over there'. It is to be hoped that the Rainbow Centre proves as solid and permanent in reality as the concept is attractive and appealing.

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Response from the authors

Dr Hobbs raises several issues; some of these concern our data and some are of more general interest. We will try to answer the former and comment on the latter.

Firstly we agree with Dr Hobbs that our figures for child abuse would be low if they represented all cases of child abuse in our catchment area. In our paper we pointed out that *'not all injured or abused children from this area are seen in the RLCH: staff in other hospitals and police stations within the area also see and diagnose child abuse'*. We also believe that due to the difficulties in collating data from several sources within the hospital our figures are incomplete.

Secondly Dr Hobbs is surprised by the absence of neglect in our series. Again in the paper we try to make clear that failure to thrive, neglect, and emotionally abused children are investigated by medical paediatricians or the mental health team. These children were not 'picked up' in our study.

Thirdly he is surprised at the low level of confirmation of diagnosis, especially in sexual abuse. As stated in the text, in physical child abuse parents and carers of children on the child protection register are very diligent about referring children for examination if they are injured. The parents do this because they fear the accusation of neglect, the carers because they are anxious not to miss a repeat of the abuse. In sexual abuse we report *'clear physical findings of child sexual abuse'* in 13% of children examined We did not analyse our findings for probability of abuse in view of the history given. We repor 19 cases of positive physical findings which would corroborate but are not diagnostic of child sexual abuse. We do not know on what grounds the diagnosis of definite or probable child sexua abuse was made in Leeds. We doubt if Hobbs is comparing like with like.

In Liverpool we do joint examinations as recommended in a British Paediatric Association/Association of Police Surgeons statement after Cleveland. The police surgeon's role is to collate forensic evidence and take part in criminal proceedings. The paediatrician's role is to see to the general care of the child and be involved in civil proceedings. In difficult cases two opinions are valuable. If only one doctor is present at the first examination, another examination may be requested by the defence. If it is granted, is this fair to the child? If it is not granted, is this fair to the defendant? Joint examinations could be carried out by two paediatricians instead of a police surgeon and paediatrician.

We agree that all paediatricians should be trained in the diagnosis of child abuse. An important function of the Rainbow Centre is medical and multidisciplinary training.

Our aim was to highlight the medical time child abuse needs to be allocated. In doing so several other issues have been aired. We will be pleased if discussion leads to more committed funding, training and medical input into this important field.

Pertussis (3): non-acceptance of vaccine

In the 1980s pertussis became more common in the United States (0·5 cases per 100 000 population in 1981 and 1·4 in 1988). A paper by Paul Etkind and his colleagues in Massachusetts (*American Journal of Diseases of Children* 1992;**146**:173–6) points to two factors possibly involved in the increase: the failure of some groups to accept immunisation for religious or other reasons and failure to accept antibiotic prophylaxis.

In four small outbreaks of the disease in Massachusetts between 1986 and 1988, 17 adults and 96 children (less than 18 years) were involved. Seventy five percent of the children had not been immunised because their parents objected on religious or philosophical grounds. Many came from families who adhered to a macrobiotic diet. In these outbreaks compliance with public health measures including the administration of prophylactic erythromycin was poor. Children who had not been immunised against pertussis were at least three times more likely than immunised children to contract the disease.

Although American children are expected to be fully immunised before they start school, most states have a religious exemption clause and during the 1980s doubts about the safety of pertussis vaccine led to more people claiming such exemption for their children. The religion seemed to be restricted to a specific article of faith in the non-acceptability of pertussis immunisation as the children were invariably fully immunised against other diseases. Public health doctors in Britain have often looked with some envy at the laws in the United States which make immunisation of preschool children compulsory but clearly compulsoriness can be a flexible commodity. Perhaps we are as well off continuing to rely on persuasion and the good sense of parents. It's against my philosophical principles to do gardening or household chores at the weekend but I'm not allowed an exemption clause. Most problems in life are amenable to good sense and negotiation (but there is wisdom in knowing when to submit!).

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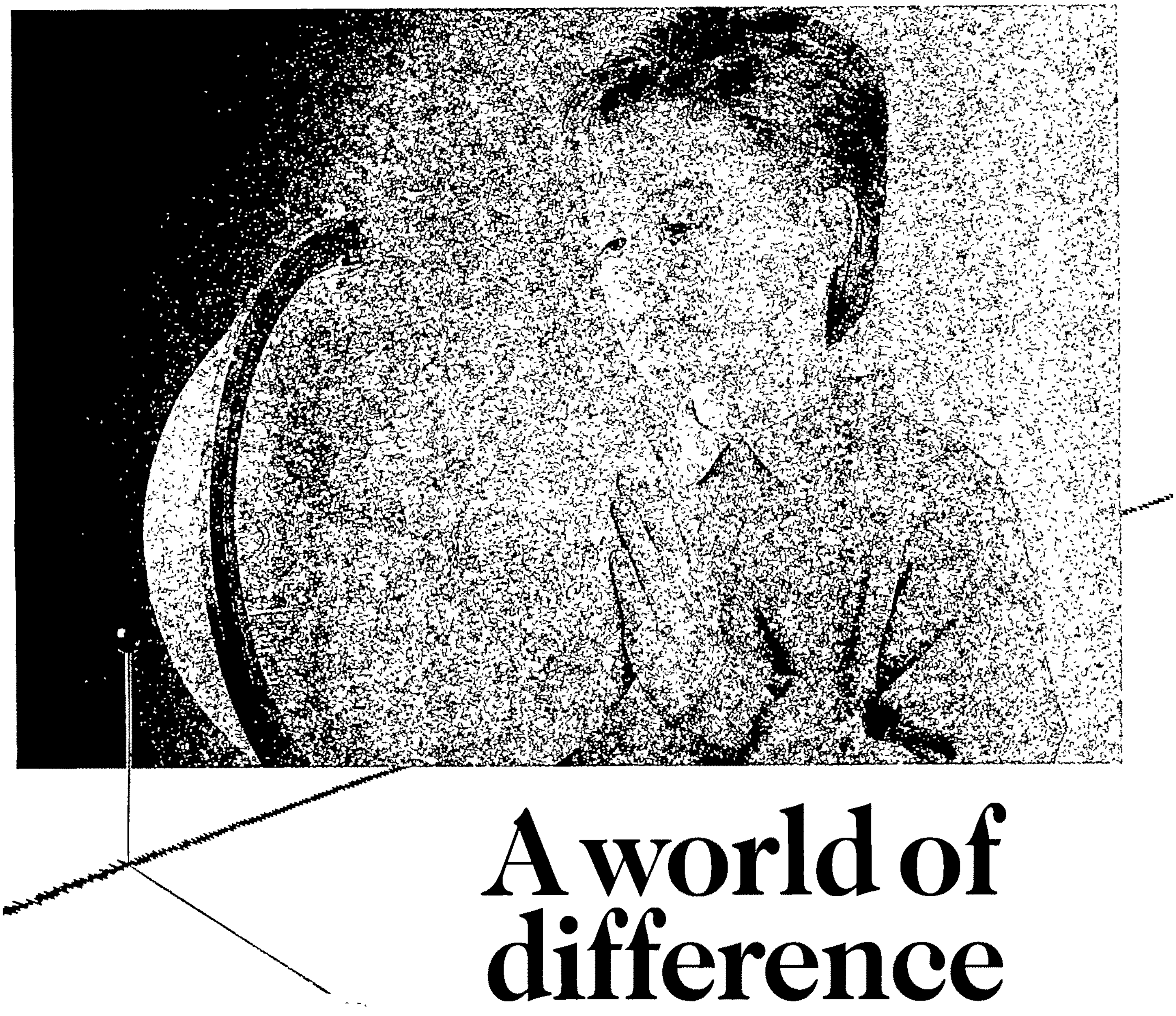

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1. Mumford JP Br J Clin Pract 1988, 42 (Suppl 61) 7-9

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Archives of Disease in Childhood 1992; **67**: 911–919

Screening of hearing impairment in the newborn using the auditory response cradle

S M Tucker, J Bhattacharya

Abstract

The Auditory Response Cradle (ARC) is a fully automated microprocessor controlled machine that was designed for the hearing screening of full term neonates. In order to evaluate the ARC, 6000 babies were screened at a district maternity hospital over a period of three years. Every infant subsequently entered a three year follow up programme.

One hundred and two babies (1·7%) failed the ARC screen (that is, they failed two ARC tests) and 20 of these were found to have some hearing impairment: in 10 it was severe (80–90 dBHL), in seven moderate (45–60 dBHL), and in three it was mild to moderate (<45 dBHL). In addition, of the 20 babies who failed a first test and were discharged before a second could be performed, two were confirmed to have a severe hearing loss; 79 infants failing the screen were cleared on further testing, giving the ARC a false positive rate of 1·3%.

On following up all 6000 infants for three years, seven children who passed the neonatal screen were subsequently found to have a hearing loss. For two babies the aetiology was unknown but for five the hearing impairment was either due to a hereditary progressive loss or definite postnatal factors. Progressive and acquired hearing losses cannot be detected at a neonatal screen and this emphasises the need for follow up screens at other stages in the child's life.

In this long term study the ARC has been found to have a high detection rate for severe hearing loss and confirms the practical possibility of using a behavioural technique for the universal screening of hearing in neonates.

The belief that the first years of life are in many ways the most critical for the development of language, and cognitive and social/emotional skills, has stimulated increasing interest in the early detection of hearing loss.[1 2] The early detection of hearing impairment is believed to be critical to optimal rehabilitative outcome[3] but incontrovertible evidence is hard to find in the literature. Some researchers have shown that the early detection of hearing impairment and provision of hearing aids assist the acquisition of language skills.[4] Other studies have shown that early fitting with hearing aids is advantageous for linguistic and cognitive development in permanent hearing loss.[5 6] Although there is little hard scientific evidence documented, most workers would agree that there is every justification for the early detection of severely and profoundly deaf infants.

In order to reduce auditory disability successfully in the first two years of life, it is important to implement screening programmes as soon after birth as possible.[7] In 1982 the Joint Committee on Infant Hearing in the United States issued a statement recommending the identification of hearing loss by 3 months of age, and no later than 6 months of age, and wherever possible the diagnostic process should be completed and habilitation begun by 6 months of age.[8] Screening for hearing loss in the neonatal period also has a distinct advantage—very early detection can be achieved on a captive population.

However, there still remain at least two unresolved issues regarding the screening of newborn infants. The first relates to whether 'universal' or 'at risk' screening should be performed. As severe congenital sensorineural hearing loss is a low incidence handicap (estimated at 1–2/1000 live births), the mass screening of all newborns is generally viewed as too time consuming and costly. Efforts at screening, therefore, generally focus on high risk groups such as neonatal intensive care unit (NICU) babies where the incidence of hearing loss is greater.[9 10]

The main problem with 'at risk' screening programmes is that they fall well short of identifying all children with hearing loss, as only approximately 50% of hearing impaired babies manifest one or more of the risk factors. In Pappas' study, only 46% of the children investigated would have been in the high risk category,[11] and in the study of Watkin *et al* of a 16 year cohort less than 40% would have been identified.[12] In the summary of a report on high risk screening programmes carried out in the United States and Canada it was recommended that universal screening should be the ultimate goal.[13] There is therefore a strong case for the universal screening of newborn infants if this could be performed reliably and cost effectively.

A second unresolved issue regarding hearing screening of the newborn is the choice of a screening technique. Three different techniques are currently available: (i) auditory evoked potential measurements, principally brainstem response audiometry,[14–16] (ii) automated behavioural assessments,[17 18] and (iii) click evoked otoacoustic emissions.[19 20]

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Accepted 19 November 1991

The three methods address different forms of auditory responses and provide varying degrees of information about the integrity of the acoustic system. In using auditory brainstem evoked potentials and otoacoustic emissions one is only analysing the intactness of the auditory system to the cochlea and brainstem respectively. Behavioural audiometry measures the responsivity of the long reflex pathway connecting the ear via the brainstem to the motor apparatus. Automated behavioural screeners therefore depend on the integrity of the entire auditory and motor systems and have the advantage of being able to establish that the whole auditory system is functioning correctly.

The Auditory Response Cradle (ARC) was designed and developed for normal term newborn screening and analyses objectively a neonate's behavioural responses to sound by comparing auditory responses during sound trials with spontaneous activity during 'no-sound' control trials.[21–24] In order to assess the feasibility of the universal screening of neonates with the ARC for congenital severe bilateral hearing loss, a long term evaluation programme was carried out on a total of 6000 infants. The babies were screened during the neonatal period and every child was then followed up for three years. This paper presents the results of this ARC evaluation programme.

Methods

THE ARC

The ARC is a fully automatic microprocessor controlled machine that was designed and developed at Brunel University over a period of 12 years to analyse objectively a normal term neonate's behavioural responses to sound. The ARC (fig 1) consists of a trolley mounted unit comprising a pressure sensitive mattress and headrest that monitor head turn, head startle, and body activity. A transducer in a polyethylene band around the baby's abdomen (over the clothes) monitors respiratory activity. The acoustic stimulus is a high pass noise (2·6–4·4 kHz) of 85 dB sound pressure level and this can be presented binaurally or monaurally to the infant via close coupled ear phones.

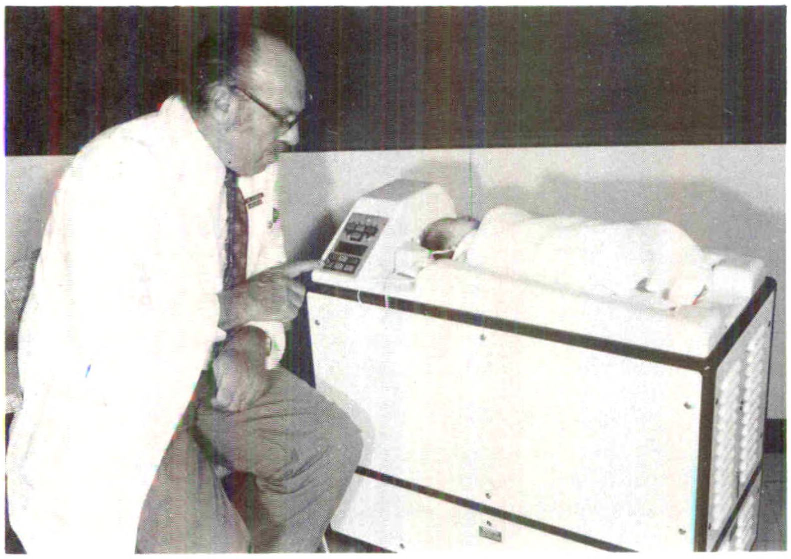

Figure 1 An infant in the ARC, model 6.

High pass noise is used because of the prevalence of high frequency impairment among the congenitally deaf. On the presentation of the sound trials, the infant's motor and respiratory responses are detected automatically and stored in the memory of the microprocessor. The presentation of an equal number of 'no sound' (control) trials enable calculation of the probability that the baby's responses to sound are specific reactions and not just spontaneous events. When this probability exceeds 97% the baby is considered to have normal responses and is 'passed'.

THE PASS/REFER DECISION

The electronics of the ARC form a hybrid computer based around the Motorolla 6800 microprocessor. As soon as the test is initiated, the sensors are continuously examined automatically. Once the baby has become relatively quiet with identifiable respiration, the microprocessor begins acquiring data for a five second prestimulus period.

A complete screening test comprises between two and 10 trial blocks, each having two sound and two control trial elements. A trial element consists of prestimulus, stimulus and poststimulus periods, each lasting five seconds. The length of the first two periods is determined by the need for at least two complete breathing cycles for analysis. The poststimulus period, together with the presentation order within the block of 'sound/sound/control/control' is believed to obviate habituation effects.

After the second trial block and subsequently after every further block, the scores to sound and control trials are compared using standard probability theory based on a binomial distribution. The PASS indicator on the control console automatically lights up when the scores differ by an amount giving a probability of at least 97% that the sound score could have been gained by pure chance. If this has not been achieved after 10 trial blocks have been presented to the infant, the REFER indicator is illuminated.

THE EVALUATION PROGRAMME

In order to evaluate the ARC as a universal hearing screener, it was recommended by the Department of Health that a mass screening programme with long term follow up should be carried out on a total of 6000 neonates. All these infants were to be screened while in the newborn nursery of Hillingdon Hospital (a district general hospital). Children failing the screen and found to be hearing impaired were to be managed by their local audiology centres. Children passing the neonatal screen were to be followed up by the ARC evaluation team at 7 to 9 months, 18 months, and 3 years of age in order to pick up any false negative cases.

The 6000 neonates in this study were tested over a three year period and represent 80·4% of the total number of live births (7462). It was not the aim to test every baby passing through the maternity unit as the ARC was only used to screen infants on three days per week. (The screening trials were carried out by two part time nursery nurses both of whom were employed for 18 hours/week.)

The neonates were screened either monaurally or binaurally on the ARC. As binaural tests were quicker they were given to babies who were not thought to be at risk for hearing impairment—that is, the majority of the 6000 infants. Neonates were tested at any time before their discharge from the maternity unit. It was found that waiting until a day or two after birth and using the period one hour after a feed to one hour before the next ensured a more settled baby. Infants from the NICU were not tested until they had reached a conceptional age of at least 42 weeks as the ARC was only designed for the screening of term babies. By waiting until this time, difficulties that might have arisen due to maturational factors and a weight below 2·27 kg were avoided. Testing was therefore only carried out on well babies.

The ARC was housed in a room at the quiet end of the antenatal ward. The test room, measuring 10×17 ft (3×5·2 m), was darkened with blinds and fitted with a sound attenuation door but was not otherwise sound treated. After obtaining informed consent for the test from the mother on the ward, the nursery nurse placed the polyethylene band containing the respiratory transducer around the infant's abdomen over the clothes. The baby was then taken to the test room in his/her bassinet and was swaddled to reduce the arousal state before being placed in the ARC. The earphones were gently put in place, and once the start button on the control console was depressed, a pass or refer decision was automatically made in 2–10 minutes. The actual test time depended on the responsiveness of the infant and in this study the shortest tests obtained were for the binaural presentation of a stimuli to term babies (approximately four minutes).

A screening failure was defined as two ARC test failures. Babies failing the ARC test on two separate occasions (on two separate days) were referred for a full paediatric examination, auditory brainstem response testing (ABR), tympanometry, and acoustic reflex measurements. On ABR testing the infant was 'cleared' if wave V was observed to have a normal latency down to a stimulus level of 30 dB normative hearing level (nHL) on each ear.

When every child initially tested at birth reached the age of 7 months (with the exception of those already confirmed as hearing impaired who were followed up separately), distraction testing was carried out by the local child health clinics. All test results were sent back to the ARC evaluation team. If the child did not attend the clinic screen a questionnaire was sent to the mother with questions about the baby's babble, awareness of sounds, and history of ear infections. Any suspicion of hearing loss arising from the returned form resulted in recall for distraction testing employing both the standard stimuli used in the clinics and warble tones of 500 Hz to 4 kHZ. The child was cleared if responses were obtained to all stimuli at a minimal level of 30 dBA on both sides (sound level measured in free field, that is room setting).

The subsequent follow up at 18 months of age took the form of a questionnaire which was sent to the mother of every child screened at birth except those already confirmed as hearing impaired. Children with unsatisfactory replies to the hearing, balance, and vocabulary questions were recalled for distraction testing, tympanometry, and acoustic reflex measurements. Stimuli employed included the cup and spoon, sibilant 'ss', high frequency rattle, voicing at low frequencies, and warble tones. Visual reinforcement audiometry was also employed when necessary and the child was cleared if he responded to all test stimuli at a minimal level of 30 dBA on both sides.

The final follow up at 3 years of age took the form of a further questionnaire. Children with unsatisfactory replies to the hearing, balance, and speech questions were recalled for pure tone headphone audiometry, tympanometry, acoustic reflex measurements, a speech discrimination test, and otoscopy. The child was cleared as having hearing within normal limits if his auditory threshold was less than 20 dBHL for 500 Hz to 4 kHz and if the audiogram was supported by the speech discrimination test (with 100% discrimination being obtained at minimal level of 35 dBA).

Audiological assessments on children recalled during the three year follow up programme were carried out in an anaechoic chamber at Brunel University. Test results were sent to the general practitioner, consultant paediatrician, ear, nose, and throat surgeon, and district community health team. At all stages of the three year evaluation programme the attendance of children recalled was 100% as transport was provided whenever necessary.

Results

The results of the long term evaluation of the ARC are shown in tables 1 to 4. Table 1 gives

Table 1 Results of ARC trials

No of neonates tested	6000
Failed first ARC test	489 (8·1%)
Passed on retest	367
Could not be retested on the ARC:	20
1 severe bilateral S/N loss (a)	
1 severe bilateral high frequency S/N loss (b)	
15 cleared	
3 lost to follow up (1 died)	
Failed first and second ARC tests:	102 (1·7%)
7 severe bilateral S/N losses	
1 severe unilateral S/N loss	
1 severe bilateral S/N loss with conductive overlay	
2 moderate unilateral S/N losses (c, d)	
1 mild/moderate bilateral S/N loss	
5 middle ear pathologies (SOM) (moderate bilateral conductive losses)	
2 ABR abnormalities (mild/mioderate bilateral S/N losses)	
1 microcephalic	
1 spastic quadriplegic (severe bilateral S/N loss)	
2 lost to follow up (1 died)	
79 cleared	(false positive rate =79/6000 = 1·3%)

S/N, sensorineural; SOM, serous otitis media.

the results of the screening trials during the neonatal stage. Tables 2, 3, and 4 give the results of the follow up programmes at 7 to 9 months, 18 months, and 3 years respectively.

RESULTS OF ARC TRIALS

Of the original 6000 neonates screened, 489 (8·1%) failed the first test but this figure was reduced to 102 (1·7%) after the second test. Seventy nine of the 102 babies referred for follow up by ABR and impedance testing were subsequently cleared, giving a false positive rate of 1·3%.

First time failures

Twenty newborn babies who failed the first ARC test were discharged from hospital before they could be tested again (table 1). One child (a) returned three weeks later and was found to have serous otitis media which was treated medically. He was subsequently tested elsewhere with electrocochleography and no action potential was observed; a severe bilateral sensorineural hearing loss was diagnosed.

The second child (b) did not return for a repeat ARC test and was lost to follow up for some time. He was eventually traced at 3 years of age when the questionnaire was returned with a comment about poor speech development. The family had moved out of the area and results from his local audiology clinic showed him to have a severe high frequency hearing loss. Of the remaining 18 infants who did not attend for retest, 15 were cleared at subsequent screens and three were lost to follow up—one died and two moved with no forwarding address.

Second time failures

Sensorineural losses—The failures at the second test (table 1) included nine babies with a severe sensorineural loss (eight bilateral, one unilateral), two with a moderate sensorineural loss (both unilateral), and one with a mild to moderate sensorineural loss (bilateral). The ABR threshold for those with severe losses was equal to or greater than 80 dBnHL. All eight children with severe bilateral sensorineural losses were issued with hearing aids.

Two children (c, d) had abnormal auditory brainstem responses on one side and no detectable responses on the other up to a stimulus level of 80 dBnHL. They subsequently attended and passed the 7 to 9 month clinic hearing screen but were nevertheless recalled for further assessment because of the ABR/distraction test disparity. Normal middle ear function was obtained on impedance testing for both children, and on distraction testing they were found to have a behavioural threshold of 30 dBA for all frequencies on the good ear and a moderate sensorineural hearing loss on the other ear. Finally, one baby was found to have a mild to moderate bilateral sensorineural loss with a threshold of approximately 40–45 dB.

Middle ear pathologies—The incidence of otitis media in a normal population of newborn infants is uncertain, inasmuch as the case material in the reports of different authors is not homogeneous.[25] In this ARC evaluation study a total of five neonates were picked up for whom subsequent testing showed a moderate bilateral hearing loss (threshold range 45–60 dBHL) which was found by tympanometry and acoustic reflex testing to be due to serous otitis media. It is not possible to know how many other babies in this study had otitis media during the neonatal period as the ARC was not designed for the detection of mild hearing loss.

Brainstem latency and rate abnormalties—Two brainstem latency and rate abnormalities were detected. One infant was born 6 weeks preterm, was severely jaundiced, and had been in intensive care for a week as a result of episodes of apnoea. No brainstem responses could be detected on the right ear up to a stimulus intensity of 80 dBnHL, and tympanometry showed middle ear dysfunction (serous otitis media). The second infant was found to have abnormal brainstem responses on both ears. On distraction testing at 8 months poorly localised 45–50 dBA responses were obtained and tympanometry showed bilateral middle ear dysfunction. As it was unclear whether the poor localisation was due to developmental immaturity or a sensorineural loss with conductive overlay, the child was retested at a later date. Both children were confirmed to have a mild to moderate (<45 dBHL) sensorineural loss.

Other abnormalities—One of the babies who failed the ARC test was subsequently found to be microcephalic. There was no indication of any high risk factors and on ABR testing normal latencies were obtained for wave V down to a stimulus level of 40 dBnHL. During ABR testing the child's electroencephalographic trace was continuously monitored. In the case of this baby it appeared abnormal and after a full paediatric assessment he was diagnosed as microcephalic. Another infant who failed the ARC test was resuscitated after apnoea and asystole: on ABR testing poor responses were

Table 2 Results of 7–9 month clinic follow up

No of children now 7 months old (18 died)	5982
Passed the clinic screen:	4917 (82·2%)
These included:	
2 moderate unilateral S/N losses (failed the ARC screen) (c, d)	
1 severe bilateral S/N loss (passed the ARC screen, aetiology unknown) (e)	
Failed the clinic screen:	14 (0·2%)
1 severe bilateral S/N loss (failed the ARC screen) (a)	
1 severe bilateral S/N loss (passed the ARC screen, aetiology unknown) (f)	
1 severe bilateral S/N loss (failed the ARC screen) (g)	
1 severe bilateral S/N loss (passed the ARC screen, progressive hereditary S/N loss confirmed) (h)	
10 cleared — 5 middle ear pathologies (SOM)	
Not tested at this screen	1051 (17·6%)
Less number of replies to questionnaire and number already confirmed as hearing impaired	992
Loss to follow up at this stage	59 (0·99%)

S/N, sensorineural; SOM, serous otitis media.

obtained for both ears. The child was subsequently diagnosed as having spastic quadriplegia with a severe bilateral sensorineural loss.

FOLLOW UP AT 7 TO 9 MONTHS OF AGE

As shown in table 2, 18 babies had died before reaching the age of 7 months. Of the 4917 babies who attended and passed the 7–9 month screen, three infants actually had some degree of hearing impairment. Two of these babies (c, d) had previously failed the ARC screen and ABR follow up. They were recalled for further assessment and were found to have a behavioural response threshold of 30 dBA for all frequencies on one side and a moderate sensorineural loss on the other (60 dBA at 500 Hz, 1 kHz, and 2 kHz; 90 dBA at 4 kHz). The third child (e) had passed both the ARC screen and the 7 to 9 month clinic screen. He was subsequently confirmed to have a severe bilateral sensorineural loss but the aetiology is unknown.

Fourteen babies failed the clinic hearing screen. This figure is very low as the child health clinics ‘passed’ all babies initially failing due to otitis media if the middle ear dysfunction had resolved on subsequent testing. The ARC evaluation team did not have the authority to ensure that only two distraction tests were carried out on each child.

Two of the 14 babies (a, g) failing the clinic screen had previously failed the ARC screen and had already been confirmed to be hearing impaired. As previously mentioned, babies with confirmed hearing loss were not entered into the 7–9 month, 18 month, and 3 year follow up programmes. However, in the case of babies a, g, c, and d the child health clinic requested them to attend the 7 to 9 month screen by mistake.

Twelve of the 14 babies failing the clinic screen had passed the ARC screen. One of these 12 (h) was tested by electrocochleography at 4 months of age as there was a history of progressive hearing loss in the family and, although the baby’s neonatal responses were fine, there was now some concern over the hearing. A severe bilateral sensorineural loss was confirmed. One child (f) failed the first ARC test and passed on retest; he was subsequently found to have a severe bilateral sensorineural hearing loss with unknown aetiology. The remaining 10 babies passed when tested again; five of them had otitis media.

There were no 7 to 9 month screening results available for 1051 children (17·6%). This category consisted of babies who had already been diagnosed as hearing impaired at the neonatal screen, and babies who were lost to follow up for reasons of refusing the test, non-attendance, moving with no forwarding address, moving out of the follow up area, and adoption. By means of a questionnaire, as already mentioned, and through an intensive search via the family doctor, the community health service, and local housing departments, all but 59 (0·99%) children were eventually traced.

Table 3 Results of 18 month follow up programme

No of questionnaires sent	5565
No returned	4164 (74·8%)
Questionnaires returned, with satisfactory replies to the hearing, balance, and vocabulary questions	4068
Babies with unsatisfactory questionnaires:	96
56 cleared	
35 middle ear pathologies (SOM)	
5 S/N losses	
1 cytomegalovirus infection	
2 meningitis with hydrocephalus	
1 Jervell and Lange-Nielsen syndrome	
1 unknown aetiology (e)	

S/N, sensorineural; SOM, serous otitis media.

FOLLOW UP AT 18 MONTHS OF AGE

A total of 5565 and not 6000 questionnaires were sent out at 18 months at this stage of the evaluation programme (table 3). There were three reasons for this: (i) questionnaires were not sent to families whose child were already diagnosed as hearing impaired, (ii) 18 children had died by the time of this follow up, and (iii) a number of families had moved with no forwarding address.

Of the questionnaires sent out, 4164 replies were received giving a 74·8% return rate. Of the questionnaires returned, 4068 gave satisfactory replies to the hearing, balance, and vocabulary questions. Ninety six children were recalled for further testing: 56 were cleared and 35 were found to have middle ear dysfunction (serous otitis media) and were referred through the consultant paediatrician and senior clinical medical officer for appropriate management.

Five children who initially passed the ARC test during the neonatal stage were found to have a sensorineural loss at this follow up. One baby with cytomegalovirus infection had his ARC test result (a ‘pass’) confirmed on the same day with ABR testing. At three months of age the ABR threshold was 45 dBnHL for the right ear and 65 dBnHL for the left. At 11 months the threshold had increased by 15 dB on both sides. This rapidly progressing sensorineural loss is a well accepted feature of virus invasion and was carefully monitored in this child.

The second child was perfectly healthy and normal at the time of the ARC test. He subsequently contracted meningitis, had a respiratory arrest at 9 weeks, and is now severely retarded with hydrocephalus and a ventricular shunt. On ABR testing, normal responses were obtained for both ears down to 20 dBnHL. However, distraction testing suggested a central loss.

The third baby showed perfectly normal responses to sound during the neonatal period. At 6 months of age he developed meningitis with subsequent hydrocephalus and at 18 months was confirmed retarded with a severe bilateral sensorineural loss.

The fourth child also showed normal responses to sound during the neonatal period but at 8 months of age Jervell and Lange-Nielsen syndrome was diagnosed and, on distraction testing, only responses to low frequencies at 90 dBA could be obtained. By 15 months of age no response could be obtained at stimulus levels up to 100 dBA.

Table 4 Results of 3 year follow up programme

No of questionnaires sent	5589
No returned	3737 (66·9%)
Questionnaires returned, with satisfactory replies to the hearing, balance, and language questions	3389
Children with unsatisfactory replies:	348
219 cleared	
128 middle ear patholgies (SOM)	
1 bilateral high frequency S/N loss (b)	

The final baby (e) passed both the ARC screen and the 7 to 9 month clinic screen. At 18 months he was confirmed to have a severe bilateral sensorineural loss. The aetiology was unknown.

FOLLOW UP AT 3 YEARS OF AGE

A total of 5589 three year questionnaires were sent out at this stage of the evaluation programme and 3737 (66·9%) were returned (see table 4). As a result of the 348 questionnaires returned with unsatisfactory replies, 347 children were recalled: 219 of these children were cleared and 128 were found to have middle ear dysfunction (serous otitis media).

The remaining child (b) had an audiogram carried out by his local audiology clinic and results indicated a severe bilateral high frequency hearing loss. This child had failed the ARC test once in the neonatal period (see table 1) and had not returned for a retest. As the family had moved outside the health district no information was obtainable on the 7 to 9 month clinic screen and the parents had not replied to the 18 month questionnaire. The child was eventually picked up via the three year questionnaire because of poor speech development.

Discussion

RESULTS OF THE ARC EVALUATION PROGRAMME

Very large numbers of babies are needed to validate fully a screening device. For this reason it was recommended by the Department of Health that a total of 6000 newborn infants should be screened with the ARC and each child should be followed up for three years.

The ARC was designed for the detection of moderate and severe hearing impairment. As can be seen from table 1, of the 102 neonates failing the ARC tests, a total of 20 babies were detected as having some hearing impairment—10 severe (80–90 dBHL), seven moderate (45–60 dBHL), and three mild to moderate (<45 dBHL). In addition, two of the 20 babies who failed a first ARC test but could not be retested were found to have a severe bilateral sensorineural hearing loss.

Estimates for the incidence of congenital hearing loss do vary. A study in the European Community gives the prevalence for losses over 50 dB in the better ear at 500 Hz, 1 kHz, and 2 kHz (in 8 year olds) as 1/1000.[26] The prevalence in a Danish study was 1·4/1000,[10] and in a study carried out in Jerusalem, 1·7/1000 for children over 5 years of age.[27] A common working estimate for the universal prevalence of severe congenital hearing loss is 1–2/1000 live births and the incidence of any degree of hearing loss[28] may be as high as 5/1000.

As can be seen from table 1, a total of 12 babies were found to have a severe hearing loss—11 bilateral, one unilateral. However, for two of these babies only one ARC test was administered as they were discharged from hospital before they could be retested. It is therefore not possible to know if they would have failed a second ARC test during the neonatal period. In this particular population of 6000 neonates the incidence of severe congenital bilateral hearing impairment appears to be 1·5/1000 (that is nine cases).

Of the 6000 neonates, 79 of the 102 who failed two ARC tests were found to have normal hearing on further testing and were subsequently cleared. This false positive rate of 1·3% is acceptably low for a screening technique and compares well with the figure of 1·5% obtained by Shepard in which the ARC was used in a modified mass screening programme.[29] The advantage of a low false positive rate is that audiological assessment facilities do not become swamped with babies requiring further testing. Unless they can cope with the additional referrals within an acceptably short time period, one only defeats the purpose of early detection. Hearing impairment should be confirmed and habilitation programmes initiated as soon as possible after the neonatal screen.

The exact number of children who lose their hearing during the first year or so of life, due to progressive or acquired losses, is unknown. One year into the ARC evaluation trials, three children who had initially passed the screen during the neonatal period were found to have a severe bilateral hearing loss (babies e, f, and h from table 2). For two of these children (e and f) the aetiology was unknown. For the third (h), the hearing impairment was due to a hereditary progressive loss. By the time every one of the 6000 infants had been followed up for three years, another four children were found to have hearing impairment—one from cytomegalovirus infection, two from meningitis with hydrocephalus, and on with the Jervell and Lange-Nielsen syndrome (table 3).

These results indicate that for five of the seven children who passed the ARC screen and were subsequently found to have a hearing loss, the loss was due to either hereditary progressive or definite postnatal factors. For this reason the 'true' number of false negative cases was possibly two and not seven. The detection of children with hearing loss subsequent to the neonatal screen highlights the importance of running screening programmes at other stages in the child's life. Progressive hearing loss and hearing impairment due to postnatal factors cannot be detected in the newborn period and children need to be followed up carefully as there will always be hearing losses that do not become evident until months or even years after birth.

In this study, automated behavioural screening with the ARC has been shown to be able to provide an early, non-invasive method of detecting hearing impairment. The evaluation programme confirms the practical possibility of using a behavioural technique for the universal screening of newborn babies.

FOLLOW UP LOSSES

During the neonatal period only five of the 6000 infants screened were lost to follow up: two babies died and three moved abroad without trace. After the neonatal period the loss to follow up increased considerably from 0·99% at 7 to 9 months to 25·2% at 18 months and 33·1% at 3 years. The only reason why follow up losses were as low as 0·99% at 7 to 9 months was because an intensive programme was carried out to trace the children via family doctor, the community health service, and local housing departments. This was extremely time consuming and would not have been possible outside a research study.

The follow up of a child subsequent to neonatal screening is one of the most difficult parts of a screening programme. This is especially so in urban metropolitan areas such as this particular district where socioeconomic and ethnic division often make recall for even routine paediatric care difficult. Also, the number of families moving with no forwarding address was particularly high and the three year loss to follow up of 33·1% was almost entirely because of this.

This particular study has incorporated a much more intensive follow up programme than other studies where newborn infants have only been followed up for a few months or a year. In order to investigate whether there were in fact any false negative cases in the group of children lost to follow up, a major study is currently being carried out involving the educational authorities and the community health services in a number of districts to try to trace these children. The aim is to reduce the present follow up loss to negligible proportions.

Follow up losses are inevitable in studies with long term evaluation programmes (despite intensive efforts to trace all children). The increasingly greater loss to follow up with time in this study reinforces the advantage of screening when the largest proportion of the population is available—that is, in the newborn nursery.

STATISTICAL PURITY OF THE PASS/REFER DECISION

The ARC uses pass/refer decision criteria which do not vary with the number of sound or control trials given. Davis showed that the statistical criteria upon which the pass/refer decision is made should take into account the varying number of trials presented to the infant.[30] However, the results in this ARC evaluation study show that the fixed criteria, for all their limitations, have correctly identified 20 babies with some hearing impairment and have only failed to identify two (if infants with acquired and progressive hearing loss are excluded).

As a separate study, over a two year period all full term neonates who required 20 or more trials to pass the ARC screen were followed up with brainstem evoked response audiometry. None of these children were found to have abnormal waveform morphology or latency intensity function. In view of these findings it is concluded that although modifications of the decision criteria could improve the statistical purity, the screening test results are unlikely to be altered with a term population.

MONAURAL VERSUS BINAURAL SCREENING

In this ARC evaluation programme the shortest test times were obtained by presenting the sound stimulus binaurally. For this reason binaural tests were given to babies who were not thought to be at risk for hearing impairment—that is, the majority of the 6000 infants. Some workers feel that if one tests binaurally and accepts that unilateral hearing losses will have a lower probability of being detected, this could lead to false assurances being offered to parents about the integrity of their child's hearing. In the study carried out by McCormick *et al* it was concluded that each ear should be tested separately.[31] This not only affords a greater possibility of detecting a unilateral condition, but gives a more thorough test for a bilateral condition.

In this ARC study it was felt that the policy of giving babies not at risk for hearing loss a binaural test did not affect the detection rate, as approximately half of the hearing impaired babies detected by the ARC were found to be in this population. These results highlight the value of a universal hearing screening programme.

The principal aim of this study was to assess the ARC's ability to detect severe bilateral hearing loss. Screening programmes may well eventually aim to detect unilateral hearing loss as data on the behavioural and linguistic manifestations of such losses indicate that these children experience more problems than previously supposed.[32]

PRACTICAL ASPECTS OF SCREENING WITH THE ARC

As already mentioned, the ARC has the advantage over electrophysiological and otoacoustic emissions techniques of assessing the integrity of a neonate's entire auditory pathway rather than just a part of it. It also has the advantages of being totally non-invasive and very acceptable to parents, of being easy to use with a simple pass or refer result, and of having a short test time when used with healthy babies. Short test times were also reported for the ARC in the modified mass screening programme carried out by Shepard.[29] Here, by not testing NICU babies until they were well, test times of four to 10 minutes were obtained on the binaural presentation of stimuli.

The time taken to test each neonate is an important consideration for any screening programme. Stevens *et al* found that screening with an evoked otoacoustic emissions technique produced a mean test time of 12·1 minutes as compared with a mean of 21·0 minutes with electrophysiological screening (ABR).[33] However, direct comparisons between the ARC and these two techniques are difficult to make as the former was used in a universal screening programme and the study of Stevens *et al* concentrated on babies taken largely from a neonatal intensive care unit. Also, it is difficult to know how much time was required in the latter study for affixing electrodes, data analysis, and other practical or administrative aspects associated with screening programmes.

In the present study, although the actual ARC test only lasted several minutes, half an hour was allocated per baby in order to allow for all the other necessary duties—for example, transporting the baby to and from the test room, preparing for the test, recording patient data and test results, and organising the management of test referrals.

THE COSTS INCURRED IN A MASS SCREENING PROGRAMME

The costs of newborn screening will vary according to the type of programme implemented. It has been felt in the past that regardless of the method used, the savings to society through early identification of hearing loss far outweigh the cost. However, today much more stringent costings are being carried out before implementing hearing screening programmes.

In this study the ARC was only used for hearing screening on three days a week and the two nursery nurses who performed the tests were employed for 18 hours a week. As there is such a rapid turnover in maternity wards today, in order to screen every newborn baby a mass screening programme would need to be in operation for five days a week. Two full time nursery nurses would be able to cover a delivery rate of 3000 a year and would ensure that a continuous screening service could be offered. Also, the employment of a part time clerk would relieve the nursery nurses of much of the record keeping and other associated paperwork that would be generated.

When implementing neonatal screening services it is very important to ensure that there is access to a well staffed audiology department so that 'screening failures' can be referred promptly for further diagnostic testing. The cost of referring these babies for further diagnostic assessment would be additional to that of the equipment and staff at the screening stage. In this study the ARC was found to have a failure rate of 8·1% after one test and 1·7% after two. By defining the overall screen failure as two test failures, screening with the ARC has been a very cost effective method of detecting hearing loss in the newborn infant. For this reason since the completion of the evaluation programme on the 6000 neonates, the ARC has continued to be used in the maternity unit for the early detection of hearing impairment.

(Screening trials in this study were carried out using the ARC model 6. This particular model is no longer being manufactured. By redesigning the ARC6 it has been possible to develop a new machine, the PARC, which is the size and shape of a large briefcase (fig 2) rather than that of a trolley mounted unit. In redesigning the machine it has been possible to reduce the purchase cost to approximately £2000.)

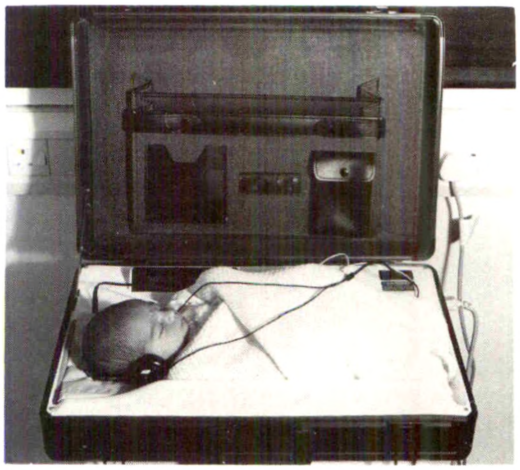

Figure 2 The PARC machine, the size of a briefcase, with the infant wearing binaural earphones.

Conclusion

The main purpose of screening for hearing impairment in newborn infants is the early detection of severe and profound bilateral sensorineural hearing loss. In this long term evaluation study of 6000 neonates, the ARC was found to have a high detection rate for this level of hearing impairment with 10 such cases having been detected after two ARC test failures. Ten babies with less severe hearing loss were also picked up. In addition, of 20 neonates failing a first ARC test who could not be retested on the ARC, two babies were found to have a severe bilateral sensorineural loss via other means.

This evaluation study of the ARC has incorporated particularly intensive follow up procedures in order that the number of false positive and false negative cases could be established as accurately as possible. A low false positive rate was obtained and this was probably because testing was only carried out on well babies. If the five children found to have hereditary progressive or acquired hearing loss are excluded, the 'true' number of false negative cases found during the three year follow up programme appears to be two. The detection of children with progressive and acquired hearing loss highlights the importance of running good follow up programmes in conjunction with any neonatal screen.

We would like to express special thanks to the nursery nurses (especially Mrs Wendy Smith) who performed all the ARC tests, and to Mr Bill Shambrook for the technical modifications of the ARC during its recent development period. (Details of the PARC may be obtained from Dr S Tucker.)

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Pertussis (4): prophylactic erythromycin

An outbreak of pertussis happended in Phoenix, Arizona in 1988 (Mary Ann Sprauer and colleagues, *American Journal of Diseases of Children* 1992;**146:**177–81). Forty percent of cases were over 7 years old. The authors examined particularly the possibly protective effect of giving erythromycin to patients and contacts. Thirty seven households with 189 members were studied and secondary spread of the disease occurred in 17 households. Most of the primary cases had been treated with erythromycin (all of those in households in which there was no secondary spread and 76% of those in households with secondary spread). Treatment was started earlier, however, in the no spread households (median 11 *v* 21 days).

There was no significant difference between the two groups (spread and no spread) as regards the proportion of household contacts given prophylactic erythromycin or the duration of prophylaxis but again there was a significant delay in giving the erythromycin to contacts in the households where secondary spread occurred (22 *v* 16 days; p=0·0008).

The authors conclude that the early administration of erythromycin to cases and contacts is effective in preventing the spread of pertussis. They recommended a 14 day course. Their data do not fill me with enthusiasm but it is a way of attempting to stop the spread of the disease.

ARCHIVIST

Archives of Disease in Childhood 1992; 67: 920–924

Growth of infants with neonatal growth hormone deficiency

J M Wit, H van Unen

Abstract

In view of contradictory reports on the growth hormone dependency of early postnatal growth we studied the growth curves of 15 infants with neonatal growth hormone deficiency. In seven infants the growth curve was parallel to the standards of the infancy–childhood–puberty (ICP) model (group 1), but in the remaining infants there was an immediate deviation of the growth curve (group 2). In this group the mean (SD) at 4 and 9 months of age was −3·3 (1·1) and −4·9 (1·4), respectively, when compared with the ICP model. The mean birth length in both groups was decreased and five out of 15 had a birth length of less than −2 SD. Serial measurements of the growth hormone response to provocation tests in two patients in group 2 showed decreasing concentrations, while four patients with documented complete growth hormone deficiency belonged to group 2. We conclude that growth hormone is needed for early infant growth and that the normal growth pattern in some infants with neonatal pituitary dysfunction is due to incomplete insufficiency.

Neonatal or congenital growth hormone deficiency has been described as a rare form of growth hormone deficiency: in two series 1·8% and 5% of growth hormone deficient patients had clinical signs shortly after birth.[1 2] The clinical presentation includes hypoglycaemia, prolonged jaundice, microgenitalia in boys, and failure to thrive. The majority of cases have multiple pituitary hormone deficiencies, particularly adrenocorticotrophic hormone (ACTH) and thyroid stimulating hormone (TSH) deficiencies, as a consequence of either hypothalamic or pituitary disease.[2 3]

There are few data on the growth pattern of infants with neonatal growth hormone deficiency. In most studies the data on length are scarce, but the observation that some children with documented growth hormone deficiency grow well in the first year of life[2 4] has led several authors to state that growth in the first six months of life may be growth hormone independent.[5 6] This concept has been used to provide a biological basis for the so called infancy–childhood–puberty (ICP) growth model which breaks down normal linear growth mathematically into three additive and partly superimposed components. The infant component is believed to be independent of growth hormone.[4 5] However, when the available case reports are scrutinised it appears that some infants were already short in length after one month or just a few months,[1 2 7 8] and in a series of 14 infants 50% are reported as having immediate growth retardation.[9]

In order to clarify this apparent discrepancy we decided to study the growth pattern from birth to three years of age in all growth hormone deficient patients who presented shortly after birth with varying combinations of hypoglycaemia, prolonged jaundice, and micropenis.

Patients and methods

All patients with neonatal pituitary deficiency including growth hormone deficiency who presented to our clinic over the previous 10 years were included, provided that sufficient growth data were available over the first nine months of life. We chose to include only those

Table 1 Clinical data. Plus or minus signs indicate the presence or absence of a condition or deficiency

Case No	Sex	Gestation (weeks)	Presentation	Asphyxia	Hypoglycaemia	Micropenis	Jaundice	Growth hormone peak in μg/l (age in months)	Additional deficiencies		
									TSH	ACTH	Prolactin
Group 1											
1	M	32	Breech	−	+	+	+	18 (1) 5 (3)	+	+	−
2	M	36	Breech	−	+	+	+	10 (2) 3 (13)	+	+	−
3	M	36	Head	−	+	−	+	1 (66)	+	+	−
4	F	35	Breech	−	+		+	1·5 (108)	+	+	−
5	F	40	Transverse	−	+		+	2·5 (13)	+	+	−
6	M	36	Breech	+	+	+	+	4·5 (12)	+	−	−
7	M	39	Head	+	+	+	+	6·5 (33)	+	+	−
Group 2											
8	M	40	Head	−	+	+	+	4 (2)	+	+	−
9	M	40	Head	−	?	+	+	<0·5 (84)	+	−	+
10	F	36	Head	−	?		+	4·5 (16)	+	+	−
11	F	40	Breech	−	+		+	1 (0·5)	+	+	−
12	F	37	Head	−	+		+	2 (21)	+	−	−
13	F	42	Head	−	+		−	6 (12)	+	+	−
14	M	40	Head	−	+	+	−	<0·5 (120)	+	−	+
15	F	42	Head	−	+		+	1 (0·5)	+	+	−

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Accepted 15 October 1991

patients with clinical signs (micropenis, hypoglycaemia, and prolonged jaundice) documenting the existence of pituitary dysfunction in utero or at least immediately after birth. Clinical details are shown in table 1.

On the basis of the presenting clinical signs, the pituitary function was evaluated. Thyroid function was assessed by measuring serum total thyroxine and free thyroxine and by the TSH response to thyrotrophin releasing hormone (TRH) in a dosage of 0·2 mg/m^2 body surface given as an intravenous bolus.

Adrenal function was assessed by measuring cortisol in at least three serum samples over 24 hours and by a short ACTH test (intravenous Synacthen 0·25 mg, Ciba Geigy). Serum prolactin was measured before and after the TRH bolus. All patients had multiple pituitary deficiencies (table 1). Two patients had an associated prolactin deficiency and TSH deficiency, which later proved to be a new hereditary syndrome.[10] Adequate hormone replacement with hydrocortisone and thyroxine was given, as soon as the diagnosis was made. The age at diagnosis was below 8 weeks of age in nine out of 15 cases. In the two groups that were formed on the basis of the growth response (see results section) four out of seven cases in group 1 and in five out of eight cases in group 2 were diagnosed before 8 weeks. Growth hormone was tested by one or two standard provocation tests if the growth velocity decreased, but in two cases had already been tested at an earlier stage. In most instances an arginine infusion test was performed using 0·5 g/kg body weight. A second test consisted either of a clonidine test (0·15 mg/m^2 body surface, given by mouth) or a sleep test (blood sampling each 20 minutes over three hours).

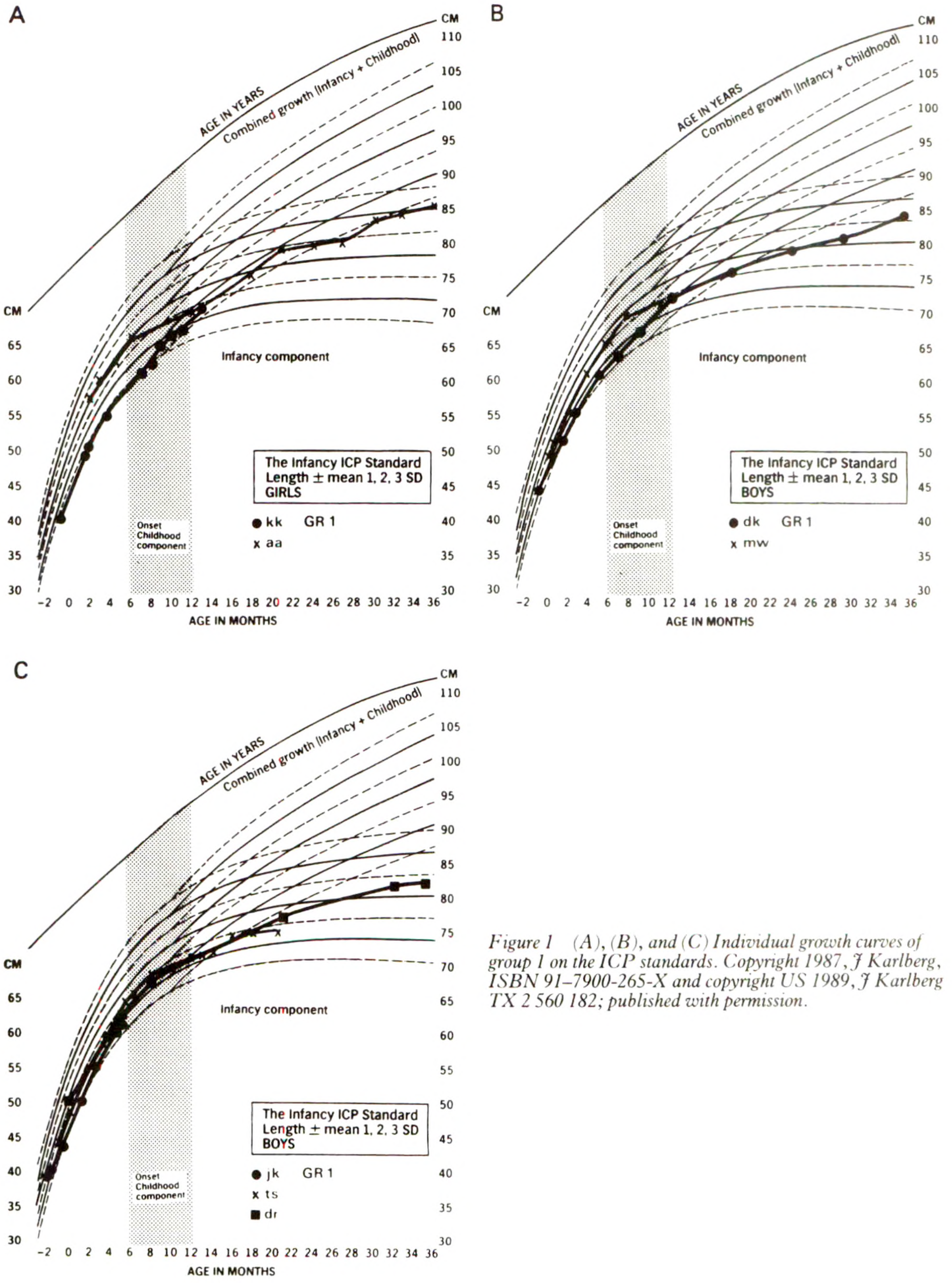

Figure 1 (A), (B), and (C) Individual growth curves of group 1 on the ICP standards. Copyright 1987, J Karlberg, ISBN 91–7900-265-X and copyright US 1989, J Karlberg TX 2 560 182; published with permission.

Individual growth curves were plotted on the ICP standard charts based on the Swedish longitudinal growth study[5] until growth hormone treatment was started. We analysed length at 0, 4, and 9 months of age. In three patients treatment was started before the age of 9 months (cases 1, 8, and 15) and in case 14 only a length at 9 months was available. Lengths at 4 and 9 months were, if necessary, estimated by interpolation.

Results

Mean birth length was diminished (table 2) and five out of 15 infants had a birth length less than 2 SD below the mean for gestational age.[11] A qualitative analysis of the growth curves showed that there were two distinct growth patterns. The first pattern was in concordance with the hypothesis that the infant component might be growth hormone independent, as the curves were parallel to the centiles up to 9 months followed by a gradual deviation (group 1, n=7). The second pattern showed a downward deviation of the growth curve from birth onwards (group 2, n=8). Individual curves are shown in figs 1 and 2 and the mean (SD) lengths at 0, 4,

Table 2 Length SD score at 0, 4, and 9 months. Values shown as mean (SD) compared with normal

	Group 1		Group 2	
	Length	No	Length	No
0 months	−1·7 (1·6)	7	−1·3 (1·4)	7
4 months	−1·5 (1·2)	7	−3·3 (1·1)	7
9 months	−1·8 (0·5)	6*	−4·9 (1·4)	6†

*One patient excluded because of growth hormone treatment.
†Two patients excluded (growth hormone treatment); in one patient length was only available at 9 months.

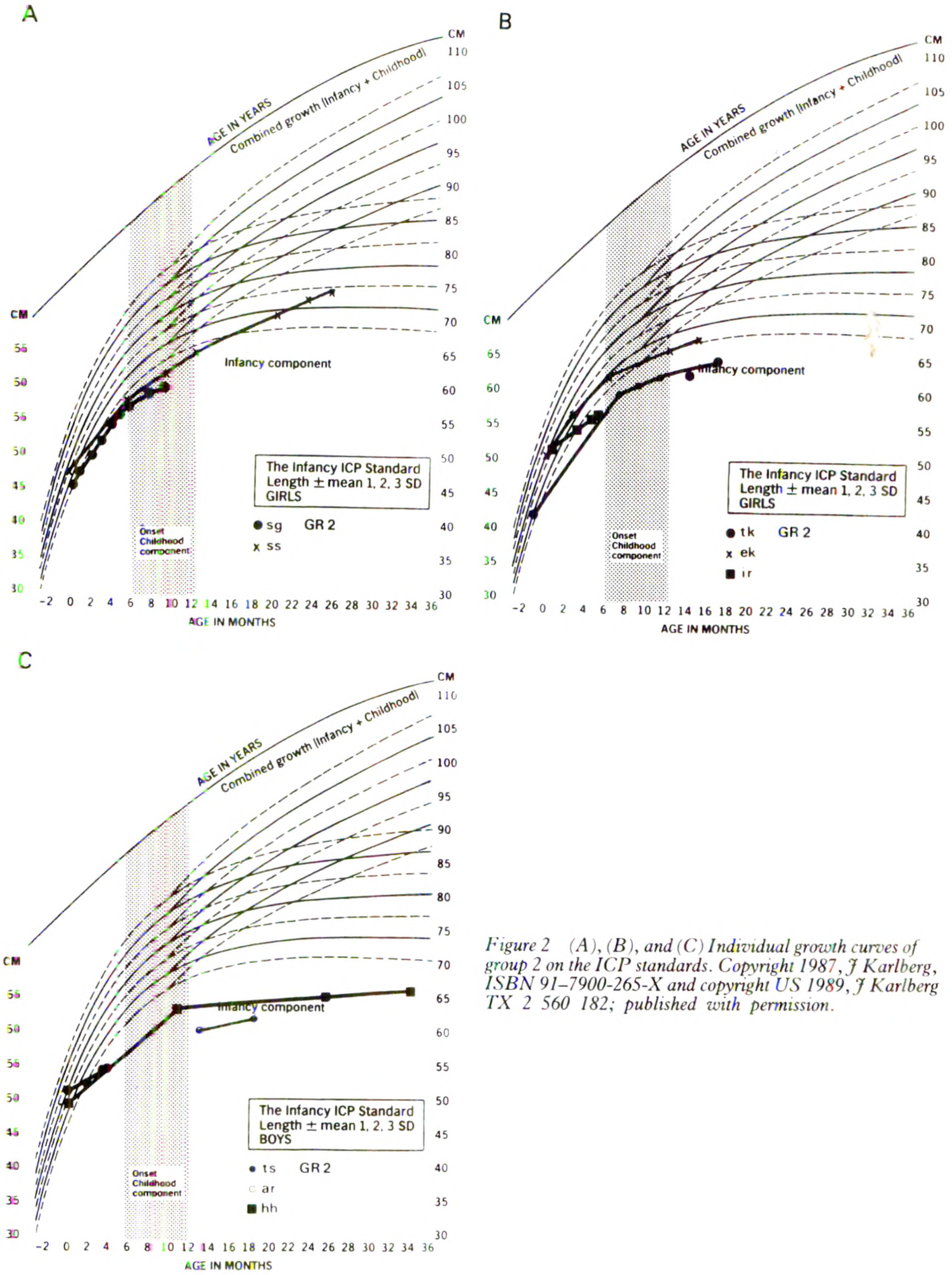

Figure 2 (A), (B), and (C) Individual growth curves of group 2 on the ICP standards. Copyright 1987, J Karlberg, ISBN 91–7900-265-X and copyright US 1989, J Karlberg TX 2 560 182; published with permission.

and 9 months of age (corrected for gestational age) are shown in table 2.

Both groups were similar in the occurrence of associated deficiencies and of presenting signs (table 1), but five out of seven infants in group 1 were born in breech or transverse position compared with one out of eight in group 2. With two exceptions, all patients had deficiencies of hypothalamic origin shown by an increased and delayed TSH response to TRH. The two patients with a total pituitary growth hormone deficiency had also a total prolactin deficiency and partial TSH deficiency.[10] These patients and two patients with a total growth hormone deficiency of hypothalamic origin detected at 2 weeks of age all belonged to group 2 (length SD score at 9 months between −7·2 and −5·3).

In two infants in group 1, two consecutive arginine tests were performed at 1–2 months and at 3–13 months showing a decreasing growth hormone peak over time (18 to 5 μg/l, 10 to 3 μg/l).

Discussion

Growth hormone is crucial for a normal statural growth during childhood, given a normal thyroid hormone secretion, but the exact age when it begins to regulate growth is uncertain. Based on few cases it has been suggested that growth hormone begins to exert a significant influence on linear growth towards the end of the first year of life.[4–6] We have shown that approximately 50% of the infants with multiple pituitary deficiencies including growth hormone deficiency indeed grow normally in the first nine months of life, which is in line with the expectations on the basis of the ICP model. However, the growth curve of the remaining infants deviated sharply from the age-references immediately after birth. In a French study of 14 infants a similar percentage was observed.[9] It is unlikely that this effect can be accounted for by the additional ACTH and TSH deficiencies, as hypocorticism and hypothyroidism were treated immediately after their appearance with appropriate dosages.

Our data are compatible with the hypothesis that some infants with neonatal panhypopituitarism do not have a complete growth hormone deficiency at birth, but develop such deficiency in the ensuing months. Of the infants who initially grew normally, two showed normal growth hormone peaks after provocation tests shortly after birth but these peaks decreased later. A similar phenomenon was observed in one out of 14 infants with neonatal growth hormone deficiency in the French study.[9] The four patients who were certainly completely growth hormone deficient at birth showed an immediate growth retardation, providing evidence that growth hormone is necessary for early postnatal growth. This observation is in line with the findings of Tanner.[12 13] While the ICP model appears to be a useful mathematical model to describe postnatal growth, the infancy and childhood components should not be associated with a growth hormone independent and growth hormone dependent growth phase, respectively.

If growth hormone is necessary for early postnatal growth, the question arises whether it might play some part in prenatal growth. So far, most authors concur that it is not necessary for prenatal growth and that insulin and insulin-like growth factors promote prenatal growth.[14] In contrast, we have shown that five out of 15 infants had a birth length of less than −2 SD and the mean birth length was −1·7 and −1·3 in the two groups. However, when all reported cases were studied, there was no infant with a birth length of less than −2 SD out of the 10 birth length measurements reported,[2 8 15–19] although a birth weight of less than 2500 g was encountered in five out 34 neonates. Recently, the study of a large database revealed that the number of infants with a short birth length was higher than statistically expected.[20] On the basis of these data it is uncertain whether growth hormone plays a part in prenatal growth and it seems more likely that the low mean birth length is caused by the additional pituitary deficiencies or by other factors not directly related to the pituitary deficiencies. All five infants with a short birth length had additional TSH and ACTH deficiencies, but this combination was also seen in the majority of the infants with normal birth lengths.

In agreement with previous studies,[1 2] we have shown that hypoglycaemia, prolonged jaundice, and micropenis are important clinical clues to the presence of hypothalamic pituitary dysfunction in the neonate. Treatment with hydrocortisone (6–12 mg/m^2/day) was in most cases sufficient to prevent further attacks of hypoglycaemia if the parents were instructed appropriately about increasing the dosage during stress. The micropenis could be treated successfully with three intramuscular injections of 25 mg testosterone esters (Sustanon, Organon).

In conclusion, this study shows that growth hormone exerts a significant influence on linear growth from birth onwards and possibly even from before birth, in contrast to earlier reports and to the assumptions made in the ICP model.

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Pain relief

What does a baby think when he (she) experiences pain? Does a baby *experience* pain or does he react to it in a reflex fashion? Does pain make a baby unhappy? Does the psychological repertoire of the newborn include happiness and unhappiness? How many angels can pirouette on a pin head?

I have referred briefly in the past (Archivist 1991: 1032) to the need for adequate analgesia for babies, quoting the work of Anand and Aynsley-Green. There seems no doubt that in the past we have all failed the babies under our care in this respect, perhaps being unduly influenced by concern about possible adverse effects of analgesia and perhaps by unanswerable philosophical speculations.

If there was any doubt remaining about the necessity for adequate analgesia for small babies it should be dispelled by another report from Dr Anand, this time with Dr P R Hickey, on work done in Boston, Massachusetts (*New England Journal of Medicine* 1992;**326**:1–9). In a prospective, randomised trial they measured hormonal and metabolic responses to cardiac surgery in 45 newborn babies, comparing two different methods of anaesthesia and analgesia. Fifteen babies received 'light anaesthesia and analgesia' with halothene, ketamine, pancuronium, and intravenous morphine during the operation and repeated morphine and diazepam postoperatively. The other 30 were given 'deep opiate anaesthesia and analgesia' using a continuous infusion of fentanyl or sufentanil and pancuronium as required. In response to surgery the babies given sufentanil produced less insulin and more adrenaline, noradrenaline, β endorphin, glucagon, corticosteroids, and aldosterone than those given halothane and morphine. Blood glucose, lactate, and acetoacetate concentrations rose to higher values in the halothane group. The chemical measurements, therefore, gave evidence of an increased stress response in the 'light anaesthesia' group. The sufentanil group also did better in terms of clinical outcome. There were no postoperative deaths in this group (n=30) but four in the halothane group (n=15). After the study mortality from open heart surgery in the Boston Children's Hospital was reduced by more than 60%. Morbidity too was significantly less in the sufentanil group in which postoperative sepsis, necrotising enterocolitis, disseminated intravascular coagulation, and metabolic acidosis did not occur whereas each of these complications occurred in 20% or more of babies in the halothane group.

So adequate anaesthesia and analgesia for babies is not only humane in that it prevents pain, it also reduces mortality and morbidity. Babies are people and people need adequate pain relief.

ARCHIVIST

Archives of Disease in Childhood 1992; 67: 925–929

Sleep related upper airway obstruction and hypoxaemia in sickle cell disease

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Accepted 23 March 1992

Abstract

A cohort of 53 patients (age range 1·9–16·5 years) with sickle cell disease (49 homozygous SS and four Sβ°-thalassaemia) was studied for evidence of sleep related upper airway obstruction (UAO). This involved (i) a clinical assessment based on a history of snoring, a score of tonsillar size, and (for 50 patients) overnight multichannel respiratory recordings, and (ii) a blinded analysis of arterial oxygen saturation (SaO_2) from the above recordings, and comparison with results from 50 healthy age matched controls of both white (n=25) and Afro-Caribbean race.

There was no difference in the baseline SaO_2 values of the white and Afro-Caribbean controls. Eighteen patients with sickle cell disease (36%) were found to have sleep related UAO. The blinded analysis showed that eight patients (16%) had episodic hypoxaemia (SaO_2 $\leq$80%, a value not observed in controls) and/or low baseline SaO_2 values (<95·8%, the lowest value seen in the controls).

Postoperative assessment was undertaken in 15 patients who underwent adenotonsillectomy. All demonstrated an improvement in symptoms and a reduction or abolition of episodic hypoxaemia. Of the 47 patients assessed when free of UAO (not demonstrated on screening, n=32, or resolved following surgery, n=15), seven continued to show baseline hypoxaemia.

Sleep related UAO and baseline hypoxaemia are common complications of sickle cell disease in children.

Sickle cell disease has an appreciable morbidity and mortality,[1–3] particularly in infancy and early childhood. There is still incomplete information, however, on the factors which increase the risk for complications of the disease, in particular the vaso-occlusive crises. The latter result from the sickling of red blood cells, after the polymerisation of deoxygenated sickle cell haemoglobin. Factors recognised as precipitating this process include dehydration, fever, acidosis, and hypoxaemia.

In recent years, there have been reports that vaso-occlusive pathology may result from undetected hypoxaemia,[4–10] in some cases secondary to sleep related upper airway obstruction (UAO). These reports include descriptions of patients who have had repeated sickle cell crises and/or cerebrovascular accidents occurring in association with severe sleep related UAO. In an attempt to determine the true incidence of UAO, populations of patients with sickle cell disease have been screened for the presence of UAO, using either questionnaires or outpatient clinical assessment.[8 9] These have revealed significant numbers of patients with a history compatible with sleep related UAO, but have not documented the prevalence of resultant hypoxaemia in patients with sickle cell disease.

To determine the prevalence of sleep related UAO and hypoxaemia, as well as its response to treatment, we studied prospectively a cohort of patients with sickle cell disease, utilising overnight sleep recordings in addition to clinical assessment. As the normal data for these studies were based on pulse oximetry values obtained in healthy children with light skin colour, we also compared recordings in black and white control children.

Subjects and methods

PROTOCOL FOR INVESTIGATION

The protocol included (i) documentation by a haematologist of signs and symptoms of UAO, (ii) overnight multichannel respiratory recordings and clinical assessment performed by a paediatric respiratory unit, (iii) examination and intervention by an ear, nose, and throat surgeon, followed by postoperative physiological recordings, and (iv) a blinded, case-controlled analysis of oxygenation from the overnight physiological recordings. Informed consent was given by all parents and, where appropriate, by the patients themselves. Ethical approval was obtained to study the controls.

SUBJECTS

The cohort under study included all patients (n=53) with homozygous sickle cell anaemia (SS) (n=49) and Sβ°-thalassaemia (n=4) over 20 months of age who were attending the Central Middlesex Hospital paediatric haematology clinic. The lower age limit was chosen to include the period of normal lymphoid tissue growth, considered to be a contributory mechanism for UAO in patients with sickle cell anaemia.[7–9] The patients were 18 boys and 35 girls, and ranged in age from 1·9–16·5 years (median 7·8).

One girl, aged 13 years, had undergone adenotonsillectomy before the study for symptoms of sleep related UAO. The remaining 52 patients had intact tonsils and adenoids. Three boys with SS had suffered cerebrovascular accidents, and an additional boy, also with SS, showed cerebral atrophy on computed tomography but without clincal signs. Another boy with SS, who was studied at the age of 4·1 years, died 1·1 years later from pneumococcal septicaemia.

CONTROLS

The controls (n=50) for the blinded analysis of oxygenation were matched to the subjects by age, resulting in median patient-control difference of 2 months (range 0 to 13). They came from two sources: (i) a random selection (n=25) from a group of healthy white children (n=45) who volunteered for previous studies. Their ages ranged from 1·9–16·3 years (median 6·9); there were 15 girls and 10 boys, and (ii) siblings (n=25) of patients with sickle cell disease who were themselves documented to be free of the disease, they were volunteers from families attending the haematology clinics at the Central Middlesex and Royal Berkshire Hospitals. Their ages ranged from 2·0–13·3 years (median 8·8); there were 14 girls and 11 boys.

CLINICAL ASSESSMENT

During haematology clinic visits, parents were asked about the presence of noisy breathing during sleep (snoring) and each tonsillar size was scored by visual examination from 0 (absent) to 6 (at the midline). UAO was considered possible in patients who snored regularly *and* whose combined tonsil size score was ≥8. These patients were referred to the paediatric respiratory unit for further assessment. All other patients without obstructive signs or symptoms were also asked if they would undergo specialist respiratory assessment in order to establish the sensitivity of an outpatient assessment in the detection of UAO. Three symptom-free patients refused respiratory assessment.

The 50 patients tested were 17 boys and 33 girls, with a median age of 8·0 years (range 1·9–16·5); 46 had SS disease and four Sβ°. Their specialist assessment followed a clinical protocol used by our group to screen children for UAO.[11] [12] This included (i) ascertainment from the parents' history whether the child showed any of the following signs during sleep: inspiratory stridor (snoring), chest wall recession, sudden wakenings with a startle or gasp, restlessness, mouth breathing, and excessive sweating; (ii) physical examination both awake and asleep, and (iii) data from a overnight tape recording of respiratory variables (see below). The latter was analysed for evidence of increased inspiratory resistance on the chest wall movement waveforms, and levels of arterial oxygen saturation (Sa_{O_2}) and end tidal carbon dioxide. The diagnosis of UAO was confirmed if there were characteristic clinical symptoms and signs, in combination with an abnormal recording, and referral was made for an ear, nose, and throat assessment. The effect of any consequent surgical intervention was checked by repeating the specialist respiratory assessment.

The 12 hour overnight tape recording performed on each subject and control comprised the following signals: (i) Sa_{O_2} from a pulse oximeter (Nellcor N-200) modified to provide beat-to-beat measurements; (ii) the photoplethysmographic pulse waveforms from which Sa_{O_2} was derived; these were used to identify and exclude Sa_{O_2} measurements associated with movement artefact; (iii) chest wall movements from respiratory inductance plethysmography (Studley Data Systems) using a purpose made vest over the chest wall (PK Morgan) and from an abdominal volume expansion capsule (Graseby Dynamics), and (iv) end tidal carbon dioxide, sampling from just below one nostril via a catheter leading to an infrared analyser (Engstrom Eliza). This last signal was measured in all patients but a minority of controls. The recording technique has been described in detail elsewhere.[11] The majority of recordings on patients was performed in hospital (82%). The remainder were carried out in the children's homes, as were those on all of the control children. The recorded signals were printed out, using an ink jet chart recorder (Siemens 34T), at 3·2 mm/second.

CASE-CONTROL STUDY OF OXYGEN SATURATION

On completion of the clinical part of the study, a blinded assessment of Sa_{O_2} was carried out on the overnight recordings of patients and controls. This was performed by two workers without knowledge of the source of the data and working to a protocol established for earlier studies.[13] [14] Breathing pattern was classified as being either regular or non-regular; regular breathing pattern was signified by periods lasting at least one minute in which breathing movements were steady in rate and amplitude; all other periods were classified as non-regular.[13] [14] Artefact on the Sa_{O_2} signal was excluded by examination of the pulse waveforms. The tracings were than examined for:

(1) *Baseline Sa_{O_2} values.* These were measured at the end inspiratory peak of five successive breaths in the centre of each period of regular pattern breathing at least 10 seconds from disturbance of the chest wall movement by sigh or apnoeic pause. The mean of these measurements was calulated.

(2) *Episodes of hypoxaemia despite continued breathing movements.* These were defined as episodes in which Sa_{O_2} fell to ≤80%; the duration of each was totalled and the frequency per hour of artefact free recording was calculated. Apnoeic pauses were identified where there was a cessation of chest wall movement with a duration of ≥4 seconds, and episodes of desaturation were discounted if they showed a temporal relationship with such pauses; that is where the beginnings of a pause in breathing and of a subsequent desaturation were separated by 2–12 seconds. This excluded the episodic hypoxaemia that has been demonstrated frequently and normally to follow apnoeic pauses in healthy infants[14] and young children, studied under a protocol identical to that used here.

The values of baseline Sa_{O_2} and episodic hypoxaemia were compared (i) between controls of different race, (ii) between patients and controls, and (iii) in patients before and after adenotonsillectomy. The significance of these differences in Sa_{O_2} were tested by Wilcoxon signed rank, Wilcoxon rank sum, or Fisher's exact tests. As evidence was already available to suggest an increased frequency of UAO in sickle cell disease one tailed tests were used for the case-control comparisons. A two tailed test was used for the comparison of oxygenation in the control groups of different race.

Results

CLINICAL ASSESSMENT

Twenty nine (55%) of the 53 patients were identified from the outpatient history and clinical examination as having symptoms and signs *suggestive* of sleep related UAO.

Eighteen (36%) of the 50 patients who underwent specialist respiratory assessment were confirmed as having UAO. Their ages ranged from 2·3–16·5 years (median 6·3). Fourteen of the 18 (78%) had been among the 29 identified at the haematology clinic; the remaining four were from the 24 patients considered from history and examination not to have UAO (8% of all patients).

Patients with documented UAO included one patient with Sβ° disease, and also two of the three who had suffered cerebrovascular accidents and the subject with cerebral atrophy. The subject who subsequently died did not demonstrate UAO at the time of the recording.

In the opinion of the ear, nose, and throat surgeons, 17/18 patients with documented UAO needed adenotonsillectomy (one patient refused an ear, nose, and throat referral); 16 have now undergone surgery (one patient refused this). Postoperative respiratory assessment was undertaken in 15 patients (one was lost to follow up); all were considered to have an improvement in clinical symptoms and signs, suggestive of complete or substantial resolution of their UAO.

CASE-CONTROL STUDY

Abnormal hypoxaemia

In eight of 50 patients, abnormal hypoxaemia was detected on recordings: all eight had baseline hypoxaemia and four also demonstrated episodic hypoxaemia. These latter four patients were also among those with the five lowest baseline values.

Baseline Sa_{O_2}

Within the control group, the median baseline Sa_{O_2} in Afro-Caribbean children was 99·2% (range 95·8–100) and in white children 99·5% (range 96·2–100; $p>0·05$ Wilcoxon rank sum).

Baseline saturation was significantly lower in the patients ($p<0·05$, Wilcoxon signed rank). The median value in the patients was 99·0% (range 88·6–100) and in the controls the median was 99·3% (range 95·8–100). Eight patients (16%) had values below the control range.

The four patients with Sβ° disease demonstrated baseline values ≥99·9%.

Episodic hypoxaemia ≤80%

Two of the 50 patients had poor quality Sa_{O_2} signals through the majority of non-regular pattern breathing. Their recordings could not therefore be included in an analysis of episodic hypoxaemia (Sa_{O_2} measurements during regular breathing were satisfactory). None of the controls, but 4/48 (8%) patients, demonstrated episodes in which Sa_{O_2} fell to ≤80% ($p>0·05$, Fisher's exact test). In these four patients the number of episodes/hour was 0·2, 0·5, 16·4, and 80·7 respectively, and these produced a totalled duration of hypoxaemia of 1·9, 2·4, 89·1, and 514·1 seconds/hour. All of these four patients had baseline Sa_{O_2} below the range in the controls.

Oxygen saturation and UAO

Thirteen patients had UAO but no evidence of hypoxaemia. The remaining five patients with UAO had abnormal hypoxaemia: four with episodic hypoxaemia plus an abnormally low baseline (88·6, 91·1, 92·1, and 93·5%), and one patient with an abnormally low baseline value alone (92·2%). Three patients thus had abnormally low baseline Sa_{O_2} without evidence of UAO (93·6, 94·1, and 95·6%). The patients with UAO had significantly lower baseline than their controls ($p<0·05$, Wilcoxon signed rank) while the difference for the 32 patients without UAO was non-significant ($p>0·05$, Wilcoxon signed rank).

In the 15 patients who were retested after adenotonsillectomy, baseline Sa_{O_2} before surgery was 88·6–100% (median 98·5%) and after surgery 90·0–100% (median 99·4%; $p>0·05$ Wilcoxon signed rank). Before surgery five patients had values for baseline Sa_{O_2} which fell below the control range; four had low values after surgery (90·0, 91·6, 94·6, and 95·0%). All four of the patients with episodic hypoxaemia ≤80% were reassessed after surgery; in two this abnormality was not identified, and in two it continued but at reduced levels (durations falling from 89·1 to 14·2, and 1·9 to 1·7 seconds/hour respectively).

Of the 47 patients tested when free of UAO, that is the group in which it was not demonstrated on screening (n=32) or the group in which it was shown to have resolved after surgery (n=15), seven patients (15%) continued to demonstrate baseline Sa_{O_2} values (90·0–95·6%) below the control range.

Discussion

Based on a history and outpatient clinical examination, 29/53 (55%) of our patients with sickle cell anaemia and Sβ° disease were considered to have symptoms and signs compatible with sleep related UAO. This agrees with the data of Wittig *et al* who, from questionnaires, found 28/65 (43%) of patients with SS disease to snore when compared with 18/102 (18%) of controls (siblings without SS).[8] Maddern *et al* found 21 out of approximately 400 (5%) children and adolescents with SS disease to have UAO. This was based on clinical assessment and confirmed by subsequent polysomnography (including measurement of oxygenation).[9] Recordings were not performed, however, on the asymptomatic patients in this cohort. Snoring and large tonsils are common, and their presence does not predict those who will have abnormal hypoxaemia.[15]

The detection of abnormalities in oxygenation is best performed by an assessment involving long term non-invasive recordings of oxygen saturation and breathing patterns. The pulse oximeters used in such studies must first have been validated against arterial line measurements. Recordings of the light plethysmograph waveforms from the pulse oximeter are required in order to identify any falls in Sa_{O_2} which are artefactual (usually due to body movements). Printouts from the oximeter which do not provide this latter signal do not allow reliable quantification of baseline hypoxaemia and the amount of episodic hypoxaemia.

Pulse oximetry has been reported to be accurate in infants and children who have sickle cell disease[16] and black skin.[17] Our study supports the latter observation by showing that healthy children with black skin have baseline Sa_{O_2} values equivalent to those of children with light skin. Pulse oximetry is reliable in SS disease because oxygenated and deoxygenated haemoglobin S have absorbances at wavelengths of light that are similar to those of haemoglobin A.[16] The oxygen dissociation curve in patients with SS disease is, however, shifted to the right, so that small falls in arterial oxygen tension may produce large changes in Sa_{O_2}.[16] It is the latter which more directly relates to the process of intracellular sickling. Pulse oximetry was therefore considered a reliable measure of clinically relevant oxygenation in this study.

In our cohort of patients with SS and $S\beta^0$ disease, 18/50 (36%) were found to have UAO documented on their overnight recording. This included 14 of the 29 considered clinically to have UAO, giving a positive predictive value of 48% and sensitivity of 78% for the 'clinical detection' of abnormalities at recording. It would be wrong to assume, however, that a history of snoring, large tonsils, and a *normal* recording mean that symptoms of UAO without blood gas abnormality are unimportant. All our patients were free of respiratory symptoms at the time of their recordings. It is possible that during respiratory infections affecting, for example, upper airway patency, physiological abnormalities such as hypoxaemia may have developed and contributed, along with fever, dehydration and acidosis, to vaso-occlusive pathology. Airway and alveolar hypoxia during infection may exacerbate intrapulmonary shunting and produce acute deteriorations in oxygenation,[18] one possible mechanism for sudden and unexpected death in young children with SS disease.[19]

We did not prospectively collect information on vaso-occlusive episodes in our patients and relate it to the results of our physiological recordings. We cannot, therefore, confirm or refute the possiblity that sickle crises are temporally associated with hypoxaemia accompanying UAO. To do this would require prospective oxygen measurements on a population of patients with sickle cell anaemia.

An examination of physiological recordings during sleep requires a knowledge of what is normal and for this reason we have collected our own control data. The recordings performed for the specialised clinical assessment were not blinded and were taken in conjunction with the history. It is possible that bias could have occurred in our interpretation of the recordings known to have been performed on the patients. The blinded, case-controlled analysis, however, helps to confirm that oxygenation problems are common in the sickle cell population (16% of the cohort had values outside control values). While a proportion of hypoxaemia is a consequence of UAO, some patients have a persistently low baseline Sa_{O_2} level which remains unexplained.

Previous studies have reported that the hypoxaemia developing during sleep in SS disease is due to hypoventilation.[5] Sleep related UAO will produce alveolar hypoventilation, the usual finding on sleep recordings being that of intermittent episodic hypoxaemia. Although baseline hypoxaemia may occur with prolonged and severe UAO, its continued presence after adenotonsillectomy in some of our patients, and its presence in three patients without UAO, suggests that chronic lung or pulmonary vascular disease may have been responsible. Wall *et al* have previously documented arterial hypoxaemia and increased calculated shunt, despite normal lung mechanics, in children with SS disease.[20] This too could represent a chronic lung disease with ventilation-perfusion mismatch similar to that found in adults with sickle cell disease.[21]

One potentially treatable cause of hypoxaemia in our patients was sleep related UAO due to enlarged tonsils and adenoids, an increasingly recognised reason for adenotonsillectomy in otherwise healthy children.[22] Although our assessment of tonsil size was not case-controlled, adenotonsillar hypertrophy may be more common in sickle cell disease. Possible explanations have included lymphoreticular hypertrophy as a result of the splenic atrophy consequent on repeated sickling in the splenic sinusoids, repeated infections or increased haemopoietic needs.[9] Evidence for the last, however, has not been borne out by examination of removed tonsils.[9] It is also possible that changes in the anatomy of the upper airway, perhaps the result of the bone marrow effects of SS disease, may produce a relative narrowing, making the child susceptible to 'normal' adenotonsillar tissue. Such anatomical abnormalities have been suggested as a mechanism for UAO.[15] Surgery to remove the tonsils and adenoids in patients with sickle cell disease has greater risks than that in otherwise healthy children, particularly in a third world setting. However, with adequate attention to hydration, temperature and oxygen monitoring, the outcome in our patients has been good. Only one of our patients underwent exchange transfusion before operation, because he had cardiac failure. This procedure is performed routinely by others.[9]

In summary, abnormal oxygenation was a common finding in a cohort of children with sickle cell disease. Where there is a history of possible sleep related UAO, or of frequent vaso-occlusive crises, such patients should undergo physiological studies during sleep to determine whether UAO and/or abnormal oxygenation is present. If UAO with episodic hypoxaemia is present, adenotonsillectomy may correct this. However a proportion of the hypoxaemia present in children with SS disease is unrelated to UAO. Further studies are required to ascertain whether baseline or episodic hypoxaemia and vaso-occlusive pathology are temporally related, thus leading to strategies that may prevent some of the morbidity and mortality associated with sickle cell disease.

We would like to thank the families who attend the haematology clinics at Central Middlesex Hospital, London, and the Royal Berkshire Hospital, Reading, the staff of these clinics, particularly Dr Carol Barton, and Mr Peter Taylor, ear, nose, and throat surgeon at Central Middlesex Hospital. We also thank Mrs Jane Lang, Dr Mark Saunders, and Mr Gary Thomson for their help in performing the recordings, Mrs Pauline Mills and Mrs Jackie Kelly for carrying out the blinded analysis, and Mr J R Alexander for statistical advice.

We would also like to thank 'Little Ones', New Moorgate Trust, Theodore Goddard, Garfield Weston, and the Priory Foundation for financial support

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Archives of Disease in Childhood 1992; **67**: 930–934

Sequelae of haemolytic uraemic syndrome

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Accepted 19 February 1992

Abstract

Twenty two patients with previous episodes of haemolytic uraemic syndrome (HUS) were investigated for evidence of deficits in cognitive, behavioural, and academic function. Patients were pair matched with 22 controls for age (±1 year), gender, and socioeconomic status. HUS patients had numerically lower cognitive and achievement scores and higher behavioural problem ratings than their controls on every measure. None of the group differences was significant at the 0·01 level. Significance values between 0·10 and 0·01 were obtained for the Wechsler full scale and verbal intelligence quotient scores and for several of the achievement measures and behaviour ratings. These results were conservatively interpreted as trends and are considered to provide preliminary indications of a post-HUS deficit in behaviour, verbal intelligence, and the verbally based skills of reading comprehension and vocabulary. The findings provide interim guidelines for follow up care but require confirmation and elaboration in a larger study.

The haemolytic uraemic syndrome (HUS) is a leading cause of renal failure in childhood, with an annual incidence of 1·44–1·74/100 000 in North American children of less than 15 years of age.[1–3] During the acute phase of the illness, some degree of central nervous system dysfunction as manifested by lethargy, seizures, or coma is observed in 33–52% of children.[1 4–8] Evidence of raised intracranial pressure is common at necropsy in children with HUS,[1 5 6 8] and postmortem examinations have demonstrated microthrombi and focal areas of infarction in the cerebral cortex.[5 9] A minority of survivors of the acute episode experience chronic seizures, developmental delay, cortical blindness, and hemiparesis.[4 6–8] It is not known whether the acute episode of HUS may also result in less severe central nervous system impairment with concomitant cognitive and behavioural deficits. This study was undertaken as a pilot investigation of the effects of an acute episode of HUS on cognitive ability, behavioural function, and scholastic achievement.

Methods

SUBJECTS

The study was carried out at the Children's Hospital of Eastern Ontario, Ottawa, and Children's Hospital of Western Ontario, Victoria Hospital Corporation, London, Ontario. Patients were eligible for the study if they met the following criteria: (a) HUS (typical diarrhoeal associated disease) diagnosed by a nephrologist; (b) onset of HUS before the age of 15 years; (c) occurrence of HUS at least six months before entry into the study; (d) current age 4 years or more; (e) first language English or French; and (f) no evidence of mental retardation (intelligence quotient (IQ)<70), documented learning disability, or other conditions associated with learning disability (for example, attention deficit disorder, cerebral palsy, meningitis, or neuromuscular disorder) before the onset of HUS. Thirty nine patients met these criteria. Of these, 22 consented to participate in the study. Seven of the remaining patients could not be located, five were no longer in the area, and five declined to participate.

Controls were selected from the patient lists of the emergency department and the paediatric nephrology clinic at the Children's Hospital of Eastern Ontario. The neuropsychological outcome measures used in this study are known to be sensitive to the influence of socioeconomic status, age, and language; this is particularly true for IQ scores which correlate positively with socioeconomic status. To ensure that patients and controls would be comparable on these important variables we first matched one clinic control to each child with HUS on the basis of age, gender, and first language. We then estimated whether each child constituted an appropriate match on socioeconomic status using data available from the postal code.[10] The latter can be linked to the median income of the households in the census district in which the individual lives. When the difference in median income of the census tracts between HUS patients and prospective matched controls differed by less than $10 000 the parents of the control subject were contacted to determine their willingness to participate in the study. Consenting parents received a telephone interview which included questions about their occupation and education. The Green socioeconomic status scale was used to confirm the match.[11]

Controls were excluded if they had chronic renal insufficiency (as defined by a creatinine value >95th centile for age), documented evidence of mental retardation, or evidence of other conditions associated with learning disability (as listed above). Emergency department controls had acute soft tissue injuries or fractured limbs (n=13). Renal clinic controls had urinary tract infections (n=5), microscopic haematuria (n=1), or minor degrees of proteinuria (n=3). There is no reason to believe that cognitive outcome measures would be affected by these conditions or their treatment.

ASSESSMENT MEASURES

Parents of children 16 years and younger completed the child behaviour checklist (CBCL)[12] and the Swanson, Nolan, and Pelham checklist (SNAP),[13] providing both a comprehensive behavioural rating and a rating of attentional deficit disorder with hyperactivity symptoms (ADD–H) listed in the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition.[14] Cognitive ability at all age levels was assessed by the appropriate Wechsler scale: the Wechsler preschool and primary scale of intelligence revised (WPPSI–R),[15] the Wechsler intelligence scale for children, revised (WISC–R),[16] or the Wechsler adult intelligence scale, revised (WAIS–R).[17] Academic achievement in children 5 years and older was measured by the wide range achievement test, revised (WRAT–R)[18] and by the brief scale of the Woodcock reading mastery test-revised (WRMT–R).[19] The spontaneous writing subscale of the test of written language 2 (TOWL–2)[20] was included in the assessment of children 7·5 years and older. These academic measures were selected to provide a brief, objective screening for problems in the core subjects of reading, spelling, mathematics, and written output.

PROCEDURES

One research assistant administered the assessment battery at both centres. The assistant was unaware of the patient/control status of the subjects and did not have access to their medical charts. Relevant medical and background information was obtained by a coinvestigator (EO) and parents were instructed not to mention the child's status during testing.

The assessment measures were carried out in a single visit for each subject and required approximately 1·5 hours for preschool children and 2·5–3 hours for older subjects. The parent accompanying the child filled in the CBCL and SNAP. No behavioural ratings were obtained for subjects 16 years and older.

Medical chart data were used to make two independent ratings of HUS severity based on central nervous system symptoms and peak creatinine values. A four point scale for central nervous system symptoms ranged from 1 (no lethargy) to 4 (coma).

DATA ANALYSIS

Paired *t* tests were carried out on all continuous assessment measures. χ^2 Comparisons and Pearson's correlations were used to analyse the relationship between HUS severity ratings and test scores. The statistical package for the social sciences (SPSS/PC+ v3·0) statistical software was used to carry out the analyses. Clinical significance was determined by a difference of at least 0·5 SD (medium effect size) or, in the case of academic tests, by a difference of at least one grade level, between the group means.

Statistical significance was interpreted conservatively. As an adjustment for multiple comparisons, $p \leq 0{\cdot}01$ was set as the criterion for significance and values between 0·10 and 0·01 were interpreted as trends.

SAMPLE SIZE AND POWER

The sample size of 44 (22 subjects with pair matched controls) was dictated by the availability of patients with HUS, and had a power of 0·79 to detect a clinically important difference between groups of 0·5 SD on the standardised tests at an alpha level of 0·05. The sample's power was 0·57 when alpha was set at 0·01.[21]

Results

SUBJECT CHARACTERISTICS

Twenty two patients and their controls participated in the study. As expected, patients and controls were well matched with regard to mean (SD) age (10·1 (4.6) *v* 10·1 (4·6) years), gender (17 females per group), and socioeconomic status (Green score, 64·1 (8·0) *v* 64·3 (8·1); $p=0{\cdot}94$).

HUS PATIENTS

Medical chart notes described all but four of the HUS patients as having some degree of lethargy during the acute phase of the illness. Five had seizures at some time, two developed hemiparesis, and two developed coma. Six patients received anticonvulsant treatment in hospital. These symptoms were slightly more severe than those of the 17 eligible patients who did not participate in the study in that none of the non-participants developed coma. None of the subjects had a creatinine concentration above 100 µmol/l at the most recent clinic visit, and no patient was being treated with anticonvulsants at the time of the assessment. Table 1 summarises the characteristics of participating HUS patients with comparison data for non-participating eligible patients and for 226 Canadian patients with HUS investigated between 1986 and 1988.[1] In general, subject characteristics are well matched in the three groups. Although the pilot study patients showed a slightly higher median age of onset, age ranges were comparable.

COGNITIVE AND BEHAVIOURAL OUTCOMES

Figure 1 illustrates the distribution of full scale, verbal, and performance IQ scores for the HUS patients and thier controls. Comparisons between the groups for these and other tests are summarised in table 2. Of note, the HUS patients obtained numerically lower mean cognitive and achievement scores and higher behavioural problem ratings than their controls on every measure.

None of the group comparisons yielded significance at the 0·01 level. Trends to significance ($0{\cdot}01>p\leq0{\cdot}10$) were obtained on several variables. Differences of this magnitude were evident on the Wechsler full scale ($p=0{\cdot}07$) and verbal ($p=0{\cdot}04$) IQ scores and on the information ($p=0{\cdot}09$), comprehension ($p=0{\cdot}03$), and vocabulary ($p=0{\cdot}02$) subtests of the Wechsler verbal

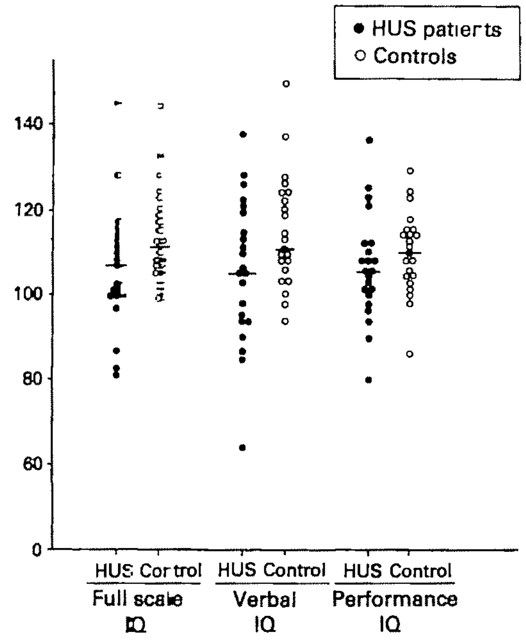
Table 1 Characteristics of the study patients

	HUS study patients 1976–90 (n=22)		Eligible non-participants (n=17)		CPKDRC subjects 1986–3 (n=226)	
	Median	*Range*	*Median*	*Range*	*Median*	*Range*
Age at HUS (years)	5·1	0·6–12	2·4	0·5–10·1	2·75	0·1–15
Peak creatinine (µmol/l)	230	53–749	274	35–1496	329	38–1492
Peak urea (mmol/l)	30·6	9·8–84·4	25·5	7·5–72·1	29·3	2·7–97·8
Lowest haemoglobin (g/l)	64	35–85	63	48–82	61	23–118
Lowest platelet (× 10⁹/l)	27	3–330*	55	18–493	34	2–430
Days in hospital	14·5	7–7	20	4–70	11	1–107
Age at testing (years)	9·7	4–2				

CPKDRC, Canadian Pediatric Kidney Disease Reference Centre
*20/22 had platelet values ≤65×10⁹/l.

scale. Differences also were found on the SNAP impulsivity subscale (p=0·10) and on the total SNAP score (p=0·10). The CBCL total score did not yield a group difference but a trend was present on the CBCL total externalising score (p=0·08). Most of the CBCL subscale patient numbers were very small as these scales vary with age level and sex. Subscales with groups of at least 15 were included in the analysis and trends were found on social withdrawal (p=0·05) and hyperactivity (p=0·07). Achievement tests yielded a trend on the WRMT–R brief scale age score (p=0·02) and on the passage comprehension subscale (p=0·07). The TOWL–2 spontaneous writing total score (p=0·06) and the contextual vocabulary subscale (p=0·05) also showed trends to significance. These trends suggest relative deficits in verbal cognitive abilities and in the related areas of word knowledge and reading comprehension as well as difficulties with the modulation of social behaviour.

There was no correlation between selected psychometric measures and age at the time of HUS, years since the HUS, or the severity of the HUS episode. Full scale mean (SD) IQ scores for HUS patients who did (n=6) or did not (n=16) develop seizures or coma showed a clinically important difference (98·3 (13·7) *v* 109·5 (13·4); p=0·12), but the statistical comparison was limited by the small number of patients with severe acute neurological symptoms. Among those with peak creatinine concentrations <300 µmol/l, only 1/16 developed seizures or coma, compared with 5/6 with a peak creatinine >300 µmol/l (p=0·002). However, there was no correlation between peak creatinine values and full scale IQ scores (r=<0·1). Similarly the correlation of hypertension and hyponatraemia with full scale IQ was not significant (r=<0·1).



Wechsler intelligence score for HUS patients and controls The horizontal lines represent median values.

*Table 2 Paired t test comparisons of cognitive, behavioural, and academic measures**

	HUS Mean (SD)	*Control Mean (SD)*	*Mean difference (SE)*	*p Value*
Weschler (n=22)†				
Verbal IQ	104·5 (16·0)	113·6 (13·5)	9·1 (4·2)	0·04
Comprehension	11·0 (2·9)	12·7 (2·0)	1·6 (0·7)	0·03
Vocabulary	10·0 (3·0)	12·1 (2·6)	2·1 (0·8)	0·02
Information	10·3 (2·6)	11·7 (3·4)	1·4 (0·8)	0·09
Performance IQ	107·6 (13·2)	110·9 (9·8)	3·3 (3·3)	0·34
Full scale IQ	106·5 (14·1)	113·9 (11·3)	7·4 (3·8)	0·07
CBCL (n=20)				
Social competence	50·7 (9·5)	51·1 (9·1)	0·4 (2·8)	0·89
Internalising total	56·2 (10·4)	50·1 (10·2)	6·1 (3·6)	0·11
Social withdrawal (n=16)	61·0 (7·9)	56·0 (3·5)	5·0 (2·3)	0·05
Externalising total	54·3 (9·9)	46·5 (11·0)	7·8 (4·2)	0·08
Hyperactivity (n=16)	61·1 (8·9)	56·1 (2·9)	4·9 (2·5)	0·07
Total behaviour problems	56·8 (11·3)	49·3 (12·2)	7·5 (4·5)	0·11
SNAP, ADD-H rating (n=20)				
Hyperactivity	0·9 (1·6)	0·3 (0·7)	0·6 (0·4)	0·13
Inattention	1·0 (1·8)	0·3 (0·8)	0·7 (0·5)	0·15
Impulsivity	1·0 (1·5)	0·3 (0·9)	0·7 (0·4)	0·10
ADD-H total	2·9 (4·2)	0·9 (2·0)	2·0 (1·1)	0·10
WRAT–R grade scores (n=19)				
Reading	5·5 (4·7)	5·9 (4·7)	0·5 (0·3)	0·20
Spelling	4·8 (4·6)	5·6 (4·9)	0·8 (0·6)	0·20
Mathematics	5·0 (4·2)	5·1 (3·7)	0·1 (0·4)	0·89
WRMT–R age scores (n=18)				
Word identification	12·5 (3·6)	13·1 (8·3)	0·5 (1·4)	0·55
Passage comprehension	13·3 (10·8)	15·1 (11·8)	1·8 (1·1)	0·07
Brief scale total	12·9 (9·6)	14·7 (10·4)	1·8 (0·9)	0·02
TOWL–2 spontaneous writing test‡ (n=15)				
Total score	34·6 (10·1)	40·2 (6·5)	5·6 (2·8)	0·06
Contextual vocabulary	7·1 (4·5)	10·4 (5·1)	3·3 (1·6)	0·05

Abbreviations: see assessment measures section in methods for test abbreviations
*Subscores are indented and are included only if p≤0·10
†WPPSI–R (n=7), WISC–R (n=13), and WAIS–R (n=2) scores were combined for analysis.
‡Scores are expressed as percentages to correct for large differences in story lengths

CLINICAL SIGNIFICANCE

Mean differences of 0·5 SD were obtained on the Wechsler verbal IQ and full scale IQ, the SNAP inattention, impulsivity, and hyperactivity scales, and on the CBCL externalising, internalising, and total behaviour problem scales as well as on several subscale measures. Differences of at least one grade level were obtained for the WRMT–R word identification, passage comprehension, and brief scale total scores.

Discussion

Central nervous system involvement is common in acute childhood HUS. In reported series, 17–24% of patients have developed seizures, 7–40% have developed coma, and up to 52% are described as lethargic in the acute phase of the illness.[1,4–8,22,23] Postulated mechanisms for the central nervous system symptoms include hypertension, hyponatraemia, or the direct toxic effects of uraemia,[8] as well as direct endothelial injury by verotoxin or Shiga-like toxin with resultant endothelial swelling and microthrombosis. Trevathan and colleagues have also demonstrated thrombotic occlusion of large branches of the anterior and middle cerebral arteries.[24] While severe chronic central nervous system impairment is known to persist in a small minority of survivors, the possible extension of milder central nervous system effects beyond the acute HUS episode has been addressed for the first time in this study.

The results of this investigation provide preliminary indications of a post-HUS deficit in verbal intelligence and in the verbally based skills of reading comprehension and vocabulary use, as well as in behaviour. These findings will require confirmation in subsequent investigations. None the less, trends emerged strongly in the present study despite the fact that only six children had seizures or coma during the acute phase of HUS, and that none of the patients had full scale IQ scores below 80.

Previous studies[1,25,26] have reported relatively high socioeconomic status for HUS patients. This finding was replicated in the present investigation in which the socioeconomic scores reflected predominantly middle to upper middle status. Because there is a positive correlation between socioeconomic status and IQ,[27] we anticipated that IQ scores would be slightly above average in our sample. This was true not for the patients but for their closely matched controls. This difference can reasonably be interpreted as an effect of HUS rather than as a flaw in case-control matching.

The possibility should nevertheless be considered that despite close matching of HUS patients and controls with regard to age, gender, and socioeconomic status we failed to achieve matching of premorbid cognitive levels. Siblings have been used to provide a more stringent control of the cognitive level before illness in studies of central nervous system dysfunction after meningitis[28] and Reye's syndrome.[29] Sibling controls were not considered appropriate for the present investigation because episodes of clinical or subclinical HUS can occur among family members and could obscure true differences on tests of cognitive function. It may be advisable to include siblings as well as pair matched controls in future studies.

The expected correlation between the severity of the acute HUS episode and the degree of central nervous system dysfunction was not evident in this study. We suspect that our sample size of 22 HUS patients together with the relatively small number of subjects with severe central nervous system involvement may have prevented detection of a true relationship. Larger studies will be required to test this hypothesis further. In our study, the trend to cognitive impairment was specific to verbal ability and related functions. If this finding is replicated it will raise important research questions concerning the reason for this functional specificity.

While our findings must be confirmed in future work, they may be considered as interim guidelines for alerting physicians to the clinically less obvious sequelae of HUS, for monitoring quality of life after recovery for the acute illness, and for making available appropriate services as needed.

This study was funded by the Children's Hospital of Eastern Ontario Research Institute Dr Peter Rowe was supported by a Career Scientist award from the Ministry of Health of Ontario We gratefully acknowledge the assistance of Esme French, research assistant, Victoria Hospital Corporation; Ruth Moffatt, Canadian Pediatric Kidney Disease Reference Centre, and of Florence Semple, Gail Emery, and the emergency room staff at the Children's Hospital of Eastern Ontario.

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Septic shock: no, no, NO

The 6 June 1991 issue of the *New England Journal of Medicine* (pages 1640–3) included an aggressive but intellectually impoverished defence of animal experimentation in medical research. Abusing animal rights campaigners, most of whom are sincere, well intentioned and non-violent, is a policy unlikely to win many friends. Animal experimentation must stand or fall on its results and its utility, that is, its relevance to human disease. It was satisfying, therefore, to see side by side in the *Lancet* of 21/28 December 1991 two papers, one describing animal experiments relating to the treatment of septic shock and the other describing the clinical application of such research in two adult patients.

There is evidence that the unresponsive hypotension of septic shock may be brought about by the accumulation in the tissues of nitric oxide (NO) which is a strong vasodilator. The NO is produced in blood vessel walls from L-arginine by the action of two enzymes (NO synthases), one physiological (called the constitutive enzyme) and one induced by the actions of endotoxin and cytokines (the inducible enzyme). Both kinds of NO synthase are inhibited by the L-arginine analogue, N^G-monomethyl-L-arginine (L-NMMA). In a study performed at the Wellcome Research Laboratories in Kent, Dr E Nava and colleagues (*Lancet* 1991;**338**:1555–7) showed that in anaesthetised rats the prolonged hypotension which followed the intravenous administration of endotoxin was prevented by giving L-NMMA intravenously in a dose of 30 mg/kg 1·5 hours after the endotoxin. The dose was critical as a low dose (3 mg/kg) had no effect and a high dose (300 mg/kg) initially raised the blood pressure but after three hours caused sudden calamitous hypotension.

At St George's Hospital in London Dr Andy Petros and his colleagues (*Lancet* 1991;**338**:1557–8) used L-NMMA and another NO synthase inhibitor, N^G-nitro-L-arginine methyl ester (L-NAME) to treat two men aged 59 and 75 years both of whom had septic shock unresponsive to conventional treatment and were considered unlikely to survive. In both of them the NO synthase inhibitor produced rapid reversal of hypotension and each of them was able to maintain a normal blood pressure without treatment within 48 hours. One patient survived but the other died two days later from the complications of severe sepsis.

NO synthase inhibitors are experimental, unlicensed drugs and there is some way to go before they can be proved to be of use in clinical practice but with the further development of these drugs and of the specific antibodies to endotoxin and the cytokines (see Archivist 1991:1021) some optimism about the future management of septic shock is perhaps not entirely out of place. Dead rats for live people seems to me the sort of bargain only the most incorrigible fanatic would deny.

ARCHIVIST

Archives of Disease in Childhood 1992; **67**: 935–939

Randomised trial of a ready-to-feed compared with powdered formula

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Accepted 9 March 1992

Abstract

Forty three infants were assigned randomly to a ready-to-feed infant formula or a standard formula that required reconstitution from powder. Despite similar nutrient composition of the two formulas those fed the powdered formula had significantly increased body weight and skinfold thickness gains, and became significantly heavier than a further group of 20 breast fed infants by 3 and 6 months. Of those fed the powdered formula 6/19 had become overweight (above the 90th or 97th centile) by 6 months, whereas 1/19 fed the ready-to-feed product was overweight at this age. While differences in fat absorption might have been contributory, our data suggest that errors in reconstitution of formula from powder might be the main cause for the growth differences observed. If it is appropriate to take the breast fed infant as a model, infants fed ready-to-feed formula in this study showed a more physiological pattern of growth than those fed a standard formula reconstituted from powder. These results require replication using other formulas as the findings have potentially important implications for infant feeding.

In some countries infant formulas are presented in liquid form either as a concentrate, requiring dilution, or as a ready-to-feed formulation. In Britain powdered formulas have been used traditionally. Ready-to-feed products are beginning to be introduced into this country, yet there are few clinical trial data on their use. It cannot be assumed that the physiological response in the infant fed these products would necessarily be the same as that found with standard powdered formulas. Heat treatment of a liquid preparation is different from that used for a powder and this might influence biological properties of the milk. Furthermore, reconstitution errors, reported first by Taitz and Byers in 1972,[1] by us,[2] and in a number of other studies on powdered formulas,[3–6] would not occur in a ready-to-feed diet.

In a trial on 43 babies whose mothers had already chosen to bottle feed, we randomly assigned the infants to a ready-to-feed, ultra high temperature (UHT) treated formula or to a standard powdered formula of the same macronutrient composition. As a part of this study we have examined the growth of these babies in the first six months of life and our findings are reported here.

Subjects and methods

In all, 43 healthy term infants were recruited for study after their delivery in the Rosie Maternity Hospital in Cambridge. The parents were approached on the postnatal ward within 72 hours of delivery only when the mother had already made a firm decision to bottle feed and had commenced doing so. The study was approved by the ethical committees of the Cambridge Health Authority and the Medical Research Council's Dunn Nutrition Unit.

Infants were assigned randomly to diet group using sealed envelopes. Randomisation was based on permuted blocks of variable length and was stratified by sex to ensure a similar sex distribution in each feed group. No infant with a birth weight outside 2 SDs from the mean was included (using Gairdner-Pearson reference data[7]). Of the infants studied, 21 were assigned to a ready-to-feed, UHT treated formula ('First' infant formula, Young Nutrition Ltd) and 21 were assigned a standard powdered formula available in Britain. The diets were very similar in nutrient composition both providing 1·5 g protein/100 ml and 67–68 kcal (280–284 kJ)/100 ml (see table 1 for macronutrient composition). In view of the difference in presentation of the two diets and the need to provide different instructions for their use it was not possible for

Table 1 Composition of the two formulas

Constituents/100 ml	*Powder formula*	*Ready-to-feed formula*
Macronutrients.		
Protein (g)	1 5	1 5
Casein:whey ratio	40 60	40 60
Fat (g)	3·6	3·6
Carbohydrate (g)	7 3	7 2
Type	100% lactose	100% lactose
Energy (kcal)*	67·6	67 2
Potential renal solute load (mosmol/l)	97	100
Minerals		
Sodium (mg)	18	19
Chloride (mg)	40	40
Potassium (mg)	65	80
Calcium (mg)	54	40
Phosphorus (mg)	27	34
Magnesium (mg)	5	6
Iron (mg)	0 5	0 7
Copper (μg)	40	40
Zinc (mg)	0·4	0·4
Iodine (μg)	7	7
Vitamins		
A (retinol, μg)	80	80
B1 (thiamin, μg)	40	60
B2 (riboflavin, μg)	100	130
Niacin (mg)	0 4	0·5
B6 (pyridoxine, μg)	40	50
B12 (cyanocobalamin, μg)	0·2	0 2
Folic acid (μg)	10	10
Pantothenic acid (mg)	300	230
Biotin (μg)	1·5	1 2
C (ascorbic acid, mg)	8	8
D3 (cholecalciferol, μg)	1 1	1 0
E (d-α-tocopherol, mg)	1·1	1·0
K (phytomenadione, μg)	5	5

*100 kcal=418 kJ.

the principal field worker (SL) to be blind to dietary assignment.

Infants were monitored at recruitment and at 1, 2, 4, 6, 10, 12, and 26 weeks of age. Further data are being collected currently beyond this period. Monitoring at one or more of these periods included (i) collection of demographic and clinical data; (ii) use of the doubly labelled water method to measure total energy expenditure and energy intake; (iii) measurement of sleeping energy expenditure by indirect calorimetry; (iv) measurement of activity using actometers; (v) assessment of bowel habit, stool volume, and stool consistency; (vi) bacteriological monitoring of the milks when prepared for use; (vii) collection of data on the accuracy of feed reconstitution in the powder formula fed group[2]; and (viii) application of detailed questionnaires to parents. Anthropometry (the focus of this paper) was performed at all the above time periods and included measurement of body weight to the nearest 10 g (using a Seca instrument, model 724), length to the last completed mm (using a Holtain Infantometer), head circumference to the last completed millimetre (using paper tape), and triceps and subscapular skinfold thickness to the nearest 0·1 mm (using Holtain skinfold calipers).

Statistical comparisons were made using Student's *t* test.

Results

There was no difference in mean (SE) birth weight or gestation between infants fed ready-to-feed milk and those fed powdered formula: respectively 3440 (110) g compared with 3480 (100) g and 40·0 (0·2) weeks and 39·5 (0·3) weeks. Both groups had similar numbers of boys and girls. All infants were born vaginally and none had severe birth asphyxia (Apgar score <5 at 5 minutes). One infant, on powdered milk, dropped out of the study at 1 week on account of kidney disease and data are not included in the analyses. Four further infants dropped out as a result of the parents' wish to change formula between 3 weeks and 6 months, three in the ready-to-feed milk group and one on powdered formula (difference in drop out rate not significant). The wish to change formula was no different from that expected from our previous field studies and was usually attributed to minor feeding problems, including possetting. Thus, by 6 months, there were 19 infants in each feed group.

Figure 1 shows the longitudinal changes in weight length, head circumference, and skinfold thickness (triceps plus subscapular). Only weight was recorded at birth; the other measurements were recorded from one week onwards. While length and head size followed a very similar pattern in the two groups, the infants fed the powdered formula developed a higher body weight and skinfold thickness during the first six months. Although the difference between groups in body weight and skinfold, shown in fig 1, did not reach significance at the 5% level at any individual time point, there were significantly faster increments in these measurements during the six month period (see table 2).

Longitudinal changes in SD scores for body weight are shown (both sexes combined) in fig 2. These were calculated (courtesy of Drs T Cole and A Paul) using the Cambridge reference growth centiles for normal infants.[8] Though infants fed the ready-to-feed milk had weight SD scores that remained close to or slightly above 0 (50th centile), the infants fed the powdered formula had a mean SD score which rose to over 0·6 by 6 months (close to the 75th centile). SD scores for head size and body length were generally close to 0 and not different between feed groups.

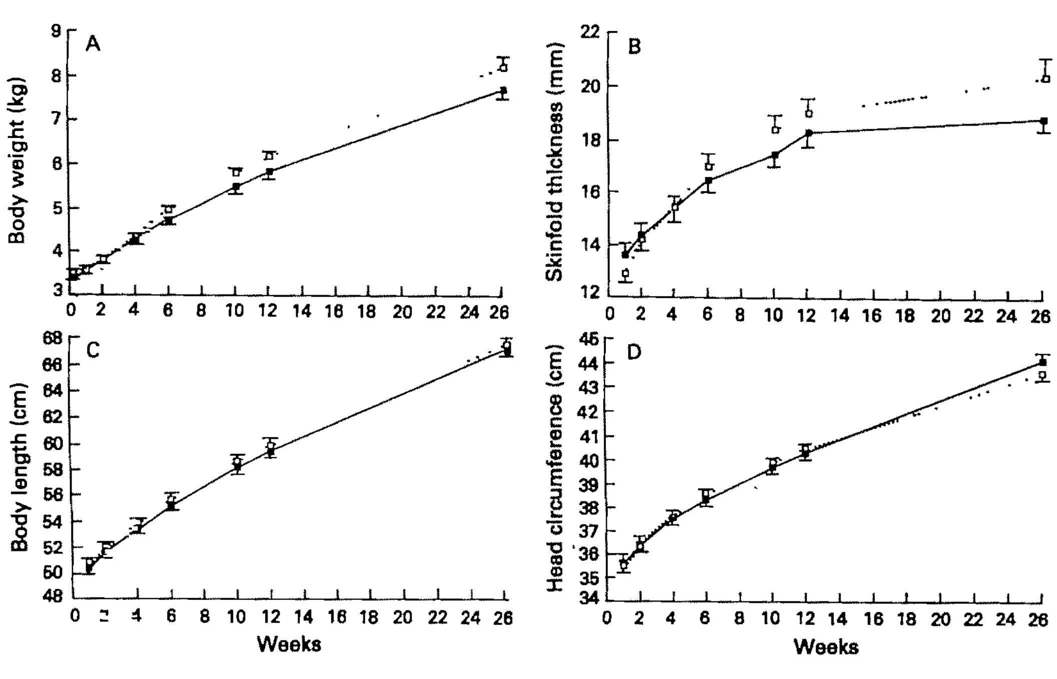

Figure 1 Longitudinal pattern of growth in infants fed a ready-to-feed formula (closed squares, solid line) or reconstituted powdered formula (open squares, dotted line): (A) body weight, (B) triceps plus subscapular skinfold, (C) length, and (D) head circumference. Data are mean (SE).

Mean data for body weight in 20 breast fed babies that we recruited.[9] [10] in the same catchment areas at 6, 12, and 26 weeks were compared with corresponding values from babies in the two formula fed groups in this study (see table 3). There were no differenes in body weight at these three ages between breast fed babies or those fed ready-to-feed formula. However, at both 12 and 26 weeks, babies fed the powdered formula were significantly heavier than those who had been breast fed.

Table 4 shows that by 6 months, six out of 19 babies fed on the powdered formula were overweight (>90th or 97th centile for by weight with normal lengths) compared with only one baby in the ready-to-feed formula group. The six babies who became overweight in the powdered formula fed group had a mean (SE) birth weight of 3497 (20) g, which was no different from the mean birth weight of the remaining infants in that feed group.

Milk volume intake on the two formulas was obtained by weighing all formula consumed for a one week period at 5 weeks and again at 11 weeks. There was no significant difference in formula intake at either period (table 5).

We explored the possibility that the greater body weight gain in the powdered formula group was related to formula reconstitution errors. On average on five occasions, at about two weekly intervals, the field worker on this project (SL) obtained a bottle of reconstituted formula provided by mothers whose babies were in the powdered milk group. The mothers were unaware of the purpose of this sampling. Milk potassium concentration was used to calculate formula strength, expressed in terms of kcal per 100 ml of formula (expected value was 68 kcal (284 kJ)/100 ml). These data have been published,[2] but were re-examined in this study in relation to the attained body weight at 26 weeks in the powder formula group. Eighteen of the subjects had both a weight measurement at 6 months and an estimate of average milk energy based on the mean of the samples taken. A linear relationship between body weight at 6 months and the average milk energy did not reach significance at the 5% level. When subjects were divided, however, into two groups, the heaviest and lightest babies, milk energy was found to be significantly higher in the heaviest babies (see table 6).

Table 2 Increments in body weight and skinfold thickness (triceps plus subscapular) in 19 infants fed a ready-to-feed (RTF) formula versus 19 fed a powdered formula. Data are mean (SE)

(A) Body weight increment

Age range (weeks)	*Diet group*	*Total gain for period (kg)*	*Average gain/ day (g)*	*Significance (p value)*
1–6	RTF	1·16 (0·07)	33 (2)	0·003
	Powder	1·42 (0·04)	41 (1)	
1–12	RTF	2·25 (0·08)	29 (1)	0·03
	Powder	2·60 (0·08)	34 (1)	
1–26	RTF	4·13 (0·18)	24 (1)	0·06
	Powder	4·67 (0·18)	27 (1)	

(B) Skinfold thickness increment

Age range (weeks)	*Diet group*	*Total gain for period (mm)*	*Average gain day (g)*	*Significance (p value)*
1–6	RTF	2·9 (0·4)	0 58 (0·07)	0·04
	Powder	4 0 (0·4)	0·81 (0·08)	
1–12	RTF	4·5 (0·5)	0 41 (0·04)	0·05
	Powder	6·0 (0·5)	0 54 (0·05)	
1–26	RTF	5·4 (0·5)	0 21 (0·02)	0·02
	Powder	7·5 (0·7)	0 30 (0·03)	

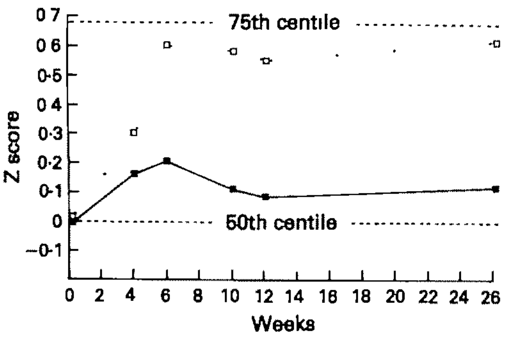

Figure 2 Longitudinal change in weight Z score (derived from Cambridge reference data[9]) for infants fed a ready-to-feed formula (closed squares, solid line) or a reconstituted powdered formula (open squares, dotted line).

Table 3 Body weight compared in breast fed infants and in those fed ready-to-feed or powdered formula. Data in kg are expressed as mean (SE)

Age (weeks)	*Breast fed (n=20)*	*Ready-to-feed (n=19)*	*Powder (n=19)*
6	4 79 (0 09)	4 76 (0 13)	4·98 (0·10)
12	5 78 (0 09)	5 83 (0 15)	6 16* (0·15)
26	7·55 (0 17)	7·70 (0·18)	8 21* (0·29)

*p<0·05 for comparison of breast fed *v* powdered formula fed.

Table 4 Infants >90th centile of weight for age by 6 months among 19 infants fed ready-to-feed formula and 19 infants fed a powdered formula

Diet	*Sex*	*Body weight (kg) at 6 months*	*Centile*
Ready-to-feed formula	F	9·40	>97th
Powder	F	8 82	>90th
Powder	F	9·34	>97th
Powder	F	9 44	>97th
Powder	M	9 55	>90th
Powder	M	9·54	>90th
Powder	F	9 92	>97th

NB. Birth weight of ready-to-feed formula fed baby 3820 g and mean birth weight of powdered formula fed infants· 3500 (SE 200) g

Table 5 Mean (SE) milk intakes in g/day by weighing

	Ready-to-feed formula (n=19)	*Powder formula (n=19)*
At 5 weeks	810 (23)	801 (29)
At 11 week	881 (34)	795 (32)†

†Not significant

Table 6 Weight at 6 months in relation to strength of reconstitution of powdered formula (as determined by potassium concentration and based on an average of five samples per case taken at intervals of two weeks). Formula strength expressed in kcal/100 ml (SE); manufacturers intended energy content=68 kcal (284 kJ)/100 ml[1]

Body weight category	*No of subjects*	*Mean body weight in kg (SE)*	*Mean milk energy content in kcal/100 ml (SE)†*
<8 kg	9	7·19 (0·17)	67·3 (1 7)
>8 kg	9	9·08 (0 17)	73 3 (1·6)†

[1] 100 kcal=418 kJ

†Milk energy in >8 kg body weight group significantly higher (p=0 02) than in the <8 kg group.

Discussion

Manufacturers of infant formulas have attempted to copy the macronutrient composition of breast milk. It might be expected therefore that infants fed modern formulas should show patterns of growth, similar to those seen in the breast fed baby. In this randomised study, however, we found that infants fed a standard formula reconstituted from powder had a significantly faster weight gain than that of infants fed a ready-to-feed formula of the same protein and energy content, and with similar contents of other nutrients. That this faster weight gain in the powdered formula fed group reflected greater body fatness was indicated by the higher rate of skinfold thickness gain, while head circumference and length gains were identical on the two formulas. Furthermore, unlike those fed the ready-to-feed formula, the powdered formula group had a higher body weight than that of a reference breast fed group at postnatal ages 3 and 5 months. Also, while only one out of 19 infants fed the ready-to-feed milk was above the 90th centile for weight at 6 months, six out of 19 infants on the powdered formula exceeded this threshold and of these, three were above the 97th centile.

This relatively small study raises a number of questions. Why should two formulas with similar nutrient content but dissimilar preparation and presentation result in such different patterns of growth? What, if any, is the clinical significance of the differences observed; and do these data have potential relevance for the future design of modern infant formulas? With regard to the first question, it is possible that we have observed a chance excess occurrence of overweight infants in the powdered formula group. Against this observation was the fact that the two groups of infants had almost identical mean birth weights, that weight gain was highly significantly greater during the first six weeks (nearly 25% faster) in the powdered formula group, and that the infants on powdered formula that did become overweight by 6 months of age, as a group, did not have higher birth weights than the other infants in the study.

Assuming that the type of formula assigned was the causal factor for the differences in weight gain observed, it is possible that differences in nutrient concentrations between the two formulas were influential. However, all the nutrient concentrations selected fall within the EC guidelines. Protein and energy contents in the two diets were virtually identical, and the concentrations of minerals and micronutrient very similar. There was, however, a difference between formulas in fat blend. Although both formulas contained 3·6 g fat/100 ml and both contained a mixture of vegetable oil and milk fat, the ready-to-feed formula contained a higher proportion of milk fat and therefore, like breast milk, had a higher content of palmitic acid (16:0) and stearic acid (18:0) and a correspondingly lower proportion of oleic acid (18:1) (table 7). Nevertheless, the difference in content of these saturated fatty acids between the ready-to-feed and powdered formula only accounted for about 11% of total fatty acids. If, for instance, there was a 30% decrease in absorption of 16:0 plus 18:0 compared with 18:1, the resultant small decrease in fat absorption in the ready-to-feed formula group (less than 1 g) would theoretically be more than offset by the slightly larger volume (see below) and therefore fat intake in this group, and in any case the decrease would be too small to account for the differences in growth between groups (though data are required on fat balances to reaffirm our calculations).

Table 7 Fatty acid composition of the ready-to-feed and powdered formula

	% Of all fatty acids	
	Ready-to-feed	*Powder*
C4:0 Butyric	3·1	—
C6:0 Caproic	1·8	—
C8:0 Caprylic	1·0	1·5
C10:0 Capric	2·1	1·3
C12:0 Lauric	2·3	9·3
C14:0 Myristic	7·8	4·5
C16:0 Palmitic	22·4	18·1
C18:0 Stearic	11·0	3·9
Other saturated fatty acids	1·1	0·4
C18:1 Oleic	25·3	44·9
C18:2 Linoleic	13·9	11·2
C18:3 α-Linolenic	2·5	2·2
Other unsaturated fatty acids	5·8	2·7

We considered the possibility that the two formulas could have had a differential impact on appetite and that the increased body fatness in the powdered formula group might therefore have been explained if they had consumed an increased volume intake. However, the data obtained by weighing the formula consumed over one week periods did not show a difference in milk volume intake between groups, and indeed the ready-to-feed formula fed infants had, if anything, a higher intake. The required heat treatment of powdered milk is necessarily quite different from that of a liquid. The UHT treatment of the ready-to-feed formula we used here would be less severe and theoretically would be expected to have less damaging effects on biologically important proteins. This might influence digestion or nutrient availability and hence the rate of weight gain.

Our data, however, provide a further, perhaps more plausible explanation for the greater fatness of babies in the powdered formula fed group. We and others have shown previously that reconstitution errors using powdered formula are common, often large, and that individual mothers rank in their tendency to over or under reconstitute the feeds they prepare.[2] Table 4 demonstrates that the heaviest 50% of babies at 6 months in the powdered formula group were given milk containing on average 6 kcal (25 kJ)/100 ml more than that received by the lightest 50% of babies at this age. In the powdered formula group the heavier babies gained weight on average at 10 g/day faster over the first six months than the lighter babies. Assuming that the samples of milk provided by the mother were representative, the heavier babies would have received up to 50 kcal (209 kJ)/day more in their diet which could explain their higher weight gain, assuming around 4 kcal (17 kJ)/g of weight gain based on our data using the doubly labelled water method.[9 10] The difference in weight gain between the babies fed ready-to-feed and powdered milk was 5 g/day averaged over the first three months and 3 g/day over the first six months. This difference could be related, theoretically, to formula reconstitution errors. Our previous work suggests that not all extra energy ingested is stored,[11] but the differences in weight gain between diet groups that we have observed could be explained by a plausible 5–7% increase in powdered formula strength over that in the ready-to-feed product, even if only 30–50% of the extra ingested energy was stored in new tissue.

As a group, babies fed powder formula approached the 75th weight centile by 6 months of age, whereas those fed ready-to-feed formula along with those fed by breast lay close to the 50th centile for this unit's reference data. It might be argued that this difference was not clinically important. Nevertheless, a greater proportion of frankly overweight infants among those given powdered rather than ready-to-feed formula could be regarded as undesirable. The difference between groups in overweight infants (6/19 compared with 1/19), though suggestive, did not reach significance at the 5% level, and a larger sample would be needed to explore this further.

Optimal patterns of growth in infancy are unknown as appropriate long term outcome studies have never been undertaken. In the absence of such data, it seems reasonable to take the breast fed baby as a model for performance. In this study, infants fed a ready-to-feed formula had a pattern of weight gain that closely resembled the physiological pattern seen in breast fed infants. In contrast, use of a powdered formula, perhaps because of the risk of formula reconstitution errors, appeared to be associated with a greater rate of fat deposition. If our data are confirmed, they would indicate a potential advantage for ready-to-feed formulations, though we recognise that currently they are too expensive for many families.

We thank Young Nutrition Limited for financial assistance and supply of the ready-to-feed formula and Evelyn Smith for her efforts in preparing the manuscript

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Archives of Disease in Childhood 1992; **67**: 940–943

Management and response to treatment of *Helicobacter pylori* gastritis

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Accepted 1 March 1992

Abstract
Gastritis associated with *Helicobacter pylori* was present in gastric biopsies from 24/95 (25%) children and adolescents undergoing endoscopy for recurrent abdominal pain and upper gastrointestinal symptoms. *H pylori* associated gastritis occurred mainly in older children (8–16 years) and was significantly associated with low socioeconomic class and a family history of peptic ulcer disease. Antral nodularity was a common endoscopic finding in *H pylori* positive children. Eighteen children, all over 5 years of age, were treated with tripotassium dicitratobismuthate (De-Nol) for two months and ampicillin for two weeks. In 12 children follow up gastric biopsies were obtained six weeks after completion of treatment. In 9/12 (75%) children *H pylori* was eradicated, and gastritis improved.

Colonisation of the stomach with *Helicobacter* (formerly *Campylobacter*) *pylori* is now firmly established as an important cause of chronic gastritis and peptic ulcer disease in adults.[1,2] Several studies have also established a role for this organism in children with abdominal pain and upper gastrointestinal symptoms.[3-5] We prospectively evaluated the prevalence of *H pylori* gastritis in children undergoing endoscopy for abdominal pain and upper gastrointestinal symptoms, and report here the clinical, socioeconomic, endoscopic and histopathological features, and the response to treatment. The systemic immune response to *H pylori* was also studied in these children and has been reported separately.[6]

Methods
A prospective study was performed between July 1987 and July 1991 on consecutive children presenting with recurrent abdominal pain, protracted vomiting, haematemesis, and melaena. Patients with recurrent abdominal pain and protracted vomiting had symptoms of at least three months' duration. Ninety five children (51 females), age range 6 months to 16 years, median 10 years, were investigated by upper gastrointestinal endoscopy and mucosal biopsy. Endoscopy was performed using Olympus GIF P3, Olympus XP20, and Fujinon UGI PE paediatric endoscopes by two paediatrician endoscopists (MJM, JML). Intravenous sedation using diazepam 0·5–1 mg/kg, maximum 25 mg, was used in 93 children; two children had endoscopy under general anaesthesia. At least two antral biopsies were taken from each child, and in 55 an additional antral biopsy specimen was taken for gastric urease (CLO test, Delta West).

Biopsy specimens were fixed in neutral buffered formalin and stained with haematoxylin and eosin for grading of gastritis and Giemsa for detection of *H pylori*.[7] All specimens were examined by one histopathogist (JIW). Gastritis was graded using the Sydney classification: briefly, this grades the degree of mononuclear cell infiltration, neutrophil infiltration, atrophy, and intestinal metaplasia in gastric biopsy specimens, each on a scale of 0–3. In addition the intensity of *H pylori* colonisation is assessed also on a scale of 0–3.[8]

Treatment with tripotassium dicitratobismuthate (De-Nol, Brocades) and ampicillin was given to children over 5 years of age with *H pylori* associated gastritis. Children with 'lymphocytic gastritis' were excluded. Eighteen children with *H pylori* associated gastritis, aged 5–15, median 12·5 years, were treated with tripotassium dicitratobismuthate for two months, and ampicillin for the first two weeks of treatment. Tripotassium dicitratobismuthate dosage was 240 mg twice daily in those over 10 years, and 120 mg twice daily in those under 10 years. The ampicillin dose was 500 mg four times a day in those over 10, and 250 mg four times a day in those under 10 years. Follow up antral biopsies were obtained six weeks after completion of treatment in 12/18 children and were assessed for eradication of *H pylori* and severity of gastritis. For the purpose of comparing biopsy specimens taken before and after treatment the grades of mononuclear cell infiltration (0–3) and neutrophil infiltration (0–3) were added to devise a gastritis score (range 0–6).

Bismuth concentrations were measured in whole blood at completion of tripotassium dicitratobismuthate treatment by hydride generation atomic absorption spectroscopy (Rooney Laboratories).[9]

Informed consent was obtained from the children's parents, and the study was approved by the hospital ethics committee of Leeds East Health Authority.

Statistical analysis was performed using Fisher's exact probability test, and Wilcoxon's signed pair test.

Results
Gastritis was present in antral biopsies from 25/95 children (26%). In 24 children (25%), age range 9 months to 15 years, median 12·5 years, chronic gastritis was associated with *H pylori*

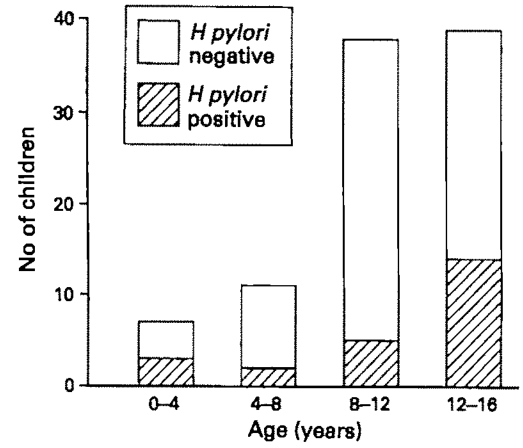

Figure 1 Age distribution of the study population

colonisation (23 histology positive; one CLO positive, histology negative). Gastric histology was normal in the other 70 children and *H pylori* was not detected on Giemsa staining or CLO test.

The CLO test was performed on 55 antral biopsies and was positive in 13. All 13 biopsies had gastritis on histology and 12/13 were positive for *H pylori* on Giemsa staining. The other 42 biopsies showed normal gastric histology and all were negative for *H pylori* on histology.

CLINICAL FEATURES

The age range of the children studied and those with *H pylori* associated gastritis is shown in figure 1. *H pylori* gastritis was present mainly in older children and adolescents aged 8–16 years, but was present in five young children aged 9 months, 15 months, 2 years, and two aged 5 years. The sex distribution of *H pylori* gastritis was 10 boys and 14 girls. A family history of peptic ulcer disease in first degree relatives was present in 6/24 (25%) *H pylori* positive children with gastritis compared with 2/70 (3%) of those who were *H pylori* negative, with normal gastric histology (p<0·003).

Although several children had multiple symptoms, the major symptom leading to endoscopy was recurrent abdominal pain. This was further subdivided into epigastric pain and central periumbilical pain. Epigastric pain was commoner in children with *H pylori* gastritis, occurring in 13/24 (54%), compared with 28/70 (40%) of those with normal histology, although this difference was not statistically significant (p=0·086). Central periumbilical abdominal pain was more common in *H pylori* negative children with normal gastric histology, 27/70 (39%), compared with 5/24 (20%) of those with *H pylori* positive gastritis, but this difference did not reach statistical significance (p=0·069). Recurrent vomiting was the second most frequent symptom but was poorly discriminatory between the two groups, being present in 4/24 (17)% and 12/70 (17%) patients with and without *H pylori* gastritis respectively. Other presenting symptoms in *H pylori* positive children were haematemesis (one child), and melaena (one child). One child with *H pylori* gastritis had refractory iron deficiency anaemia.

Social class distribution of H pylori positive and H pylori negative children

	Non-manual classes			*Manual classes*		
	1	*2*	*3NM*	*3M*	*4*	*5*
H pylori positive	0	0	3	6	7	8
	3 (12·5%)			21 (87·5%)*		
H pylori negative	3	18	6	26	8	10
	27 (38%)			44 (62%)		
Study population	3 (3·1%)	18 (19%)	9 (9.5%)	32 (33·7%)	15 (15·8%)	18 (18·9%)
	30 (31·6%)			65 (68·4%)		
West Yorkshire (1981 census)	5%	23%	12%	36%	18%	6%
	40%			60%		

*Significant difference between positive and negative groups (p<0·02)

SOCIAL CLASS

The social class of the children studied was assigned according to the occupation of the head of the household using the registrar general's classification, and is shown in the table. For purposes of comparison, non-manual classes 1, 2, and 3NM were grouped together and compared with manual classes 3M, 4, and 5. The social class distribution of the study population was broadly similar to that of the population of West Yorkshire,[10] but there was a marked social class difference between *H pylori* positive and negative children. Children of parents with manual occupations were overrepresented in the *H pylori* positive gastritis group 21/24 (87·5%) compared with 44/71 (62%) in the *H pylori* negative group (p<0·02), and no *H pylori* positive child came from social class 1 or 2.

ENDOSCOPY

Endoscopic abnormalities were present in 20/24 children with *H pylori* gastritis. The commonest abnormality was antral nodularity (fig 2) found in 13/24; five children had antral erythema and gastric erosions were present in two. Duodenal ulcers were diagnosed in two children (aged 15 and 13 years): one was associated with gastric erosions and coexistent *H pylori* gastritis on antral histology, the other was an isolated finding and was not associated with *H pylori* gastritis. The principal endoscopic finding in the *H pylori* negative, normal gastric histology group was macroscopic oesophagitis, present in 14/70, and microscopic oesophagitis was found in a further eight on oesophageal biopsy.

HISTOLOGY

Of the 25 children with chronic gastritis, 22 had typical helicobacter associated chronic gastritis on histology. Three children showed the pattern of 'lymphocytic gastritis'.[11]: one of these had helicobacter on histological staining, and one was positive on CLO test, while all three had positive *H pylori* serology.[6] Thus 3/25 (12%) of children with chronic gastritis showed this special type of gastritis, a frequency higher than

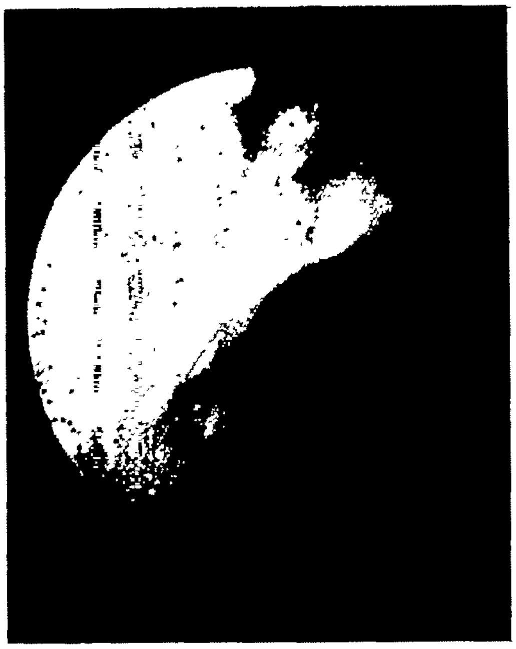

Figure 2 Antral nodularity seen at endoscopy in a child with H pylori gastritis

that seen in adults, where it is present in 2% of patients with chronic gastritis.[11] None of the biopsy specimens showed reactive gastritis or any of the other special forms of gastritis recognised by the Sydney system.

The 22 children with helicobacter associated chronic gastritis (excluding cases of lymphocytic gastritis) were graded according to the Sydney system. All showed some increase in chronic inflammatory cells, and lymphoid follicles were present in biopsies from 12/22 (55%) children (fig 3). The presence of 'activity' of chronic gastritis is assessed by the degree of neutrophil infiltration of the epithelium. This was present in specimens from 10/22 (45%) children only, although it is characteristically present in adults with helicobacter gastritis.[12]

None of the biopsy specimens showed architectural irregularity to suggest there had been any atrophy of antral glands, and none of them showed intestinal metaplasia.

RESULTS OF TREATMENT

In the 12 children in whom antral biopsy specimens before and after treatment were studied, *H pylori* eradication was achieved in 9/12 (75%). Gastritis scores improved in the *H pylori* eradication group from mean (SD) of 2·55 (1·13) before treatment to 1 (0·5) after treatment ($p<0·025$) (fig 4). Symptoms resolved in seven children but were unchanged in two despite eradication of *H pylori* and improvement in gastritis score. In the three children in whom *H pylori* was not eradicated, gastritis score was not significantly altered, and all remained symptomatic. Six other children had identical treatment and all experienced an improvement in symptoms, but follow up endoscopy was declined by their parents. The 15 year old adolescent with duodenal ulcer and coexistent *H pylori* gastritis was treated with tripotassium dicitratobismuthate and ampicillin at doses mentioned above, and ranitidine 150 mg twice daily. Follow up endoscopy 11 months after presentation showed healing of the ulcer but mucosal biopsies were not obtained.

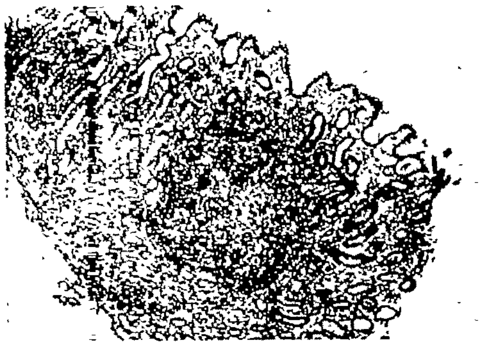

Figure 3 Lymphoid follicle in the antral mucosa of a child with H pylori gastritis.

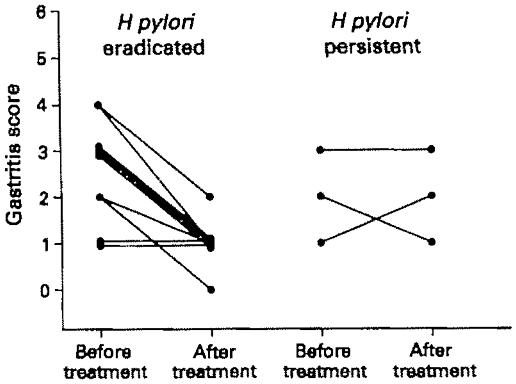

Figure 4 Severity of gastritis in antral biopsy specimens before and after treatment, showing significant reduction ($p<0·025$) in gastritis score where H pylori was eradicated.

No child developed side effects from treatment. Bismuth concentrations ranged from 3 to 29 ng/ml, mean 14·8 ng/ml. Bismuth toxity is associated with concentrations above 50 ng/ml.[13]

Discussion

This study confirms the findings of other workers that *H pylori* gastritis is a significant cause of abdominal pain in the paediatric age group.[3–5] The clinical profile of paediatric *H pylori* gastritis that emerges from this study is of epigastric pain in the older child and adolescent (8–16 years) from a family of low socioecomonic status and a family history of peptic ulcer disease. However, we have found that *H pylori* gastritis can occur in young children, and 20% of our cases were in children aged 5 years or younger. The bias towards low socioeconomic groups in *H pylori* positive children suggests that social class is a factor in *H pylori* acquisition in childhood. Children from higher social class groups appear to be less susceptible to *H pylori* infection, and similar results have been found in adults in the United Kingdom.[14] Although the reservoir of infection and modes of spread of *H pylori* are not known, the social patterns are suggestive of faecal–oral transmission, and social class differences may reflect differences in sanitation and hygienic practices.[15]

Positive endoscopic findings are common in children with *H pylori* associated gastritis, especially antral nodularity. Lymphoid follicles were present in biopsies from 55% children; the presence of follicles was not correlated with the activity of the gastritis, nor the density of bacterial colonisation. As the antral mucosa in children is thinner than that in adults, it is likely that the presence of large lymphoid follicles accounted for the nodularity apparent on endoscopy.

Lymphocytic gastritis is an unusual pattern of inflammation in adults, but was seen rather more frequently in our paediatric biopsy specimens (3/25). As in adults, these children showed serological evidence of *H pylori* infection, although the bacteria were apparent on histology in only one of three children. The relationship between lymphocytic gastritis and *H pylori* infection is still uncertain.

The precise indications for treatment and the optimal treatment regimen for children with *H pylori* gastritis remain to be established.[16] We choose treatment with tripotassium dicitratobismuthate and ampicillin as this combination gave optimal results in a large adult study.[17] We achieved a *H pylori* eradication rate of 75% and this is similar to other paediatric studies using a combination of ampicillin and bismuth preparations.[5 18] In adult studies better eradication rates have been achieved with dual therapy using a bismuth preparation and metronidazole, but there are problems with metronidazole resistance.[19] Blood bismuth concentrations were measured because of concern about potential toxicity of bismuth preparations in children, and all were in the non-toxic range. Tripotassium dicitratobismuthate was well tolerated and no child developed side effects.

The discovery of *H pylori* in 1983, and the subsequent demonstration of its role in gastroduodenal pathology, has been one the most exciting developments in gastroenterology in the past decade. Chronic abdominal pain in children has always been an important part of the paediatrician's workload.[20] This study and others suggest a role for *H pylori* in children with chronic abdominal pain and upper gastrointestinal symptoms.[3–5] Although relatively uncommon in children, a strong association exists between *H pylori* gastritis and duodenal ulceration. Furthermore, eradication of *H pylori* has been shown to improve ulcer healing and to reduce ulcer relapse rate in children.[21] The natural history of *H pylori* gastritis is still being delineated, but present evidence suggests a slow progression to atrophic gastritis and gastric atrophy over a period of 20–40 years. Atrophic gastritis and gastric atrophy are known to be precursor lesions for the development of gastric carcinoma,[22] and this potential carcinogenicity of *H pylori* makes it a significant pathogen in children.

Treatment with bismuth preparations and antibiotics can eradicate *H pylori* and improve gastritis in about 75% of patients, but long term follow up and control studies are lacking. Recent reviews have sounded a note of caution about the indiscriminate treatment of *H pylori* especially the risk of antibiotic resistance, both in children[16] and in adults.[19] Serological detection of *H pylori* IgG antibodies is valuable in screening children with chronic abdominal pain for *H pylori* gastritis,[6] and perhaps endoscopy should be reserved for detection of associated duodenal ulcer disease. Treatment to eradicate *H pylori* would then be justified in view of the role of *H pylori* in duodenal ulcer healing and relapse.[21] Further research remains to be done before we fully understand the precise role of *H pylori* in children with chronic gastrointestinal symptoms, the indications for treatment, and the optimal agents.

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Archives of Disease in Childhood 1992, 67: 944–947

Transient hypothyroxinaemia associated with developmental delay in very preterm infants

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Accepted 28 February 1992

Abstract

In 563 surviving very preterm (<32 weeks gestational age) and/or very low birthweight (<1500 g) infants the relationship between neonatal thyroxine concentration and psychomotor development at 2 years of age (corrected for preterm birth) was studied. A significant association was found between low neonatal thyroxine concentration and a negative score on the three milestones of development. These findings do not support the view that transient hypothyroxinaemia in preterm infants is harmless.

Low thyroxine concentrations are very common in the first weeks of life in preterm and low birthweight infants. The thyroxine values are inversely related to gestational age and birth weight,[1–3] and severity of respiratory and other neonatal disease.[1 4 5] Such transient hypothyroxinaemia is viewed by many as an adaptive process.[1 2 4 5] However, its significance for later development has not been established for lack of large prospective studies, and the need for thyroid hormone replacement is controversial.[6]

We used the opportunity presented by a nationwide collaborative survey on very preterm and very low birthweight infants in The Netherlands to study the relationship between thyroxine values, as measured routinely in the national screening programme for congenital hypothyroidism, and later psychomotor development of the study infants as assessed in the follow up programme.

Patients and methods

The Project on Preterm and Small for Gestational Age Infants in The Netherlands is a collaborative survey collecting data on 1338 infants, liveborn in 1983 with a gestational age of less than 32 weeks and/or a birth weight of less than 1500 g.[7 8] The surviving infants all entered a standardised follow up programme up to 2 years of age, corrected for preterm birth. Examinations were performed by the local paediatricians, and the results were recorded on precoded forms designed to minimise the risk of interobserver variability.[9 10]

Psychomotor development was assessed at the corrected age of 2 years, using the Gesell test adapted for Dutch children (revised Van Wiechen test) after oral and written instruction following the standardised guidelines for this test.[11 12] For the present study, the items obtained by history were omitted because of possible bias in reporting from the mother. The three developmental milestones chosen for analysis were obtained by direct observation of the child: 'builds tower of three blocks' (fine motor behaviour and coordination), 'walks without support' (gross motor function), and 'puts ball in box upon request' (passive language). Each of these milestones is reached at the age of 24 months by 90% of a group of normal children.[11]

These items were chosen as indicators of the effect of transient hypothyroxinaemia on development on theoretical grounds: the effect of a noxious influence on the developing nervous system depends on the postconceptional period in which the nervous system is exposed.[13] The postconceptional period of transient hypothyroxinaemia in the study group resembles the period of prenatal hypothyroidism in early treated (before the age of 1 month) term born patients with congenital hypothyroidism. Prenatal hypothyroidism (retarded bone age, more marked hypothyroidism at birth) increases the risk of developmental delay at the age of 1·5 to 3 years—that is, a delay in psychomotor development which is not confined to one field of behaviour.[14–18] Therefore, based on this analogy, the chosen measure of developmental delay in our study represents developmental delay which is not confined to one area of development: a developmental delay was assumed to be present when at least one of the three selected milestones was not reached.

Although the national screening programme for congenital hypothyroidism prescribes testing between days 6 and 8, in practice only about 70% of all newborn infants are actually screened at that age; 97% are screened within 14 days from birth.[19] In preterm infants, the delay in screening is greater.

Out of 944 children assessed at the corrected age of 2 years, screening values between days 5 and 17 could be obtained and linked to the follow up data in 563 cases (of which 479 (85%) had been tested between days 6 and 11). Missing values were caused mainly by a later start in the collection of thyroxine values (mid-April) compared with the perinatal data (1 January) and missing birth weight and gestational age in screening data, prohibiting linking (n=311); missing thyroxine values because heel puncture was performed before day 5 or after day 17 (n=56); by exclusion of disabling congenital malformations (n=7), permanent primary congenital hypothyroidism (n=1), and infants with temporary thyroid hormone replacement (n=5); and unknown duration of ventilatory support (n=1). Comparison of prenatal and perinatal characteristics showed no

Table 1 Characteristics of the study group

	Study group (n=563)	*Source population* (n=953)*
Mean (SD)		
Gestational age (weeks)	31·0 (2·6)	31·0 (2·5)
Birth weight (g)	1275 (257)	1315 (283)
Highest bilirubin concentration (μmol/l)	176 (43)	178 (45)
Average increase in body weight (g/day)	20·1 (4·2)	20·2 (4·4)
Number (%)		
Male	280 (49·7)	486 (51·0)
Small for gestational age	288 (40·5)	354 (37·1)
Apgar score ≥7	471 (83·7)	792 (83·1)
Respiratory distress syndrome	221 (39·3)	371 (38·9)
Intracranial haemorrhage and/or convulsions	97 (17·2)	174 (18·3)
Septicaemia	171 (30·4)	318 (33·4)
Duration of ventilatory support (days)		
0	287 (51·0)	490 (51·4)
1–7	163 (29·0)	267 (28·0)
8–28	95 (16·9)	165 (17·3)
≥29	18 (3·2)	31 (3·3)

*Project on preterm and small for gestational age infants.[7–10 12 24–26]

important differences (table 1), and therefore we assume that no selection bias has occurred.

Thyroxine values were measured as part of the national screening for congenital hypothyroidism.[20] In addition, a second measurement of thyroxine was performed on special request for the present study in 443 infants between 18 and 39 days of age. Thyroxine concentrations from filter paper eluates were determined in duplicate by radioimmunoassay[21] in five laboratories with permanent laboratory quality control,[22] each with an average of 125 samples per day. Thyroxine in the eluates was expressed as standard deviations about the mean calculated on a daily basis.[23] When appropriate, thyroxine (T4) values have been calculated using a regression equation ($T4\ (SD) = -4{\cdot}065 + 0{\cdot}0184 \times T4$ nmol/l), based on a correlation of simultaneously obtained blood spot thyroxine and serum thyroxine in 115 low birthweight infants on the seventh day of life, determined in the same laboratory.[1]

The relationship between thyroxine concentration and developmental outcome was studied using cross tabulations as well as multivariate stepwise logistic regression analysis with unconditional maximum likelihood estimation PROC LOGIST, Statistical Analysis System. Possible confounding factors were agreed before analysis, based on clinical experience and literature[7–9 24–26]: infant's sex, gestational age, birth weight, weight for gestational age (<10th centile),[27 28] Apgar score at 5 minutes (<7), age at thyroxine screening (in days), and highest observed neonatal serum bilirubin concentration (μmol/l). Covariables, related to neonatal disease, were: intracranial haemorrhage (clinical diagnosis based on rapid or saltatory deterioration, fall in erythrocyte sedimentation rate, and/or ultrasound or computed tomography),[24 26] seizures (irrespective of duration), respiratory distress syndrome (clinical diagnosis based on the need for extra oxygen for more than 24 hours, expiratory grunting, tachypnoea, sternal and intercostal retractions and nasal flaring, and/or typical radiograph),[26] and sepsis (haematological findings of typical white cell count and/or positive blood culture).[26]

To control for severity of disease, two additional variables were included in the analysis: ventilatory support (total number of days of intermittent positive pressure ventilation or continuous positive airway pressure) which indicated the severity of respiratory disease, and the mean weight gain during hospital stay (g/day). Finally, a separate analysis was done in the subset of 228 infants in which grading of intracranial haemorrhage according to Papile[29] was possible.[24]

The adjusted odds ratios are derived from logistist regression including all confounding factors listed above.

All statistical tests were two sided and a p value of less than 0·05 was considered to be significant.

Results

Mean thyroxine concentration in the 563 study infants was −2·4 (recalculated as 91 nmol/l), which is considerably below the mean (SD) of the total screened population, which by definition is 0 (1 SD), or 221 (54) nmol/l. The range was −5·0 to +0·5 SD.

Psychomotor development, as assessed by the three items described, was normal in 473 (84%) of the children, scoring all items positively. No relation was found between thyroxine and any of the three items separately. However, there was a significant association between thyroxine concentration and the number of children scoring negatively on at least one of the three items. Crude risks, odds ratios, as well as adjusted odds ratios, showed a linear increase of risk (table 2).

Assuming a linear relation, the overall crude odds ratio (not adjusted for potential confounding) for 1 SD decrease in thyroxine was 1·4 ($p<0{\cdot}01$), implying a 40% increase in the odds that developmental delay will occur. After adjusting for the potential confounders, as mentioned in the patients and methods section, the odds ratio did not change appreciably, neither after adjusting for each covariable separately

Table 2 The association of thyroxine and psychomotor development (n=563)

Thyroxine (SD)	*Calculated thyroxine (nmol/l)*	*Psychomotor development*		*Risk*	*Odds*	*Crude OR**	*Crude overall OR*	*OR computed by regression analysis*		
		Normal	*Delay*					*Without adjusting*	*Adjusted†*	*Adjusted overall OR by 1 SD (95% CI)*
≥−1·0	≥164	41	3	0·07	0·07	—		—	—	
−1·1 to −2·0	110–163	121	15	0·11	0·12	1·7	1·4	1·2	1·1	1·4‡ (1·1 to 1·9)
−2·1 to −3·0	56–109	177	38	0·18	0·21	2·9		2·0	1·9	
≤−3·1	≤55	134	34	0·20	0·25	3·5		3·5	3·5	

OR, odds ratio.
*Relative to the group with thyroxine ≥−1·0 SD, test for trend, p=0·003
†Adjusted for possible confounding factors, mentioned in the patients and methods section
‡p=0·01.

nor after adjusting for all covariables simultaneously The overall adjusted odds ratio was 1·4 (95% CI 1·1 to 1·9). In the subset of 228 infants with a known degree of intracranial haemorrhage,[24] the crude adjusted odds ratios were the same as in the total study group; including the degree of intracranial haemorrhage in the analysis did not alter the odds ratio. Within the group of 90 children with developmental delay (at least one negative item), no relation was found between thyroxine concentration and number of negative items (Kruskall–Wallis one way analysis of variance $p>0·5$).

Discussion

This study shows an association between thyroxine concentration and later psychomotor development in very preterm and very low birthweight infants who, having survived the first few days of life, took part in the national screening programme for congenital hypothyroidism. Even after adjusting for a number of obvious possible confounding factors representing degree of prematurity and severity of neonatal disease, a significantly increased risk of developmental delay was found in children with relatively lower neonatal thyroxine concentrations.

Preterm birth and severity of neonatal disease are known to be associated with both lower thyroxine values and poor developmental outcome.[2 5] Therefore a major concern in this study was to preclude the possibility that the observed association between lower thyroxine and development delay was an artefact, with a common cause (preterm birth, neonatal disease). In our data, the overall odds ratio remained entirely unaffected after adjusting simultaneously for the carefully selected potential confounders, which virtually precludes the possibility of substantial residual confounding of this overall association. The 13 potential confounders which were included represent immaturity and neonatal disease. It is hardly imaginable that some fourteenth confounder would be able to cause any appreciable shift in the thyroxine developmental odds ratio after adjustment for 13 other confounders.

The systematic increase in the risk of developmental delay with decreasing thyroxine concentrations suggests the possibility of a causal relationship. The available literature on the essential function of thyroid hormones in growth and developmental of the nervous system[30–36] supports such a hypothesis. Thyroxine and triiodothyronine act on brain development and maturation by binding to triiodothyronine nuclear receptors. Serum thyroxine is the major source of brain triiodothyronine: approximately 70–80% of the triiodothyronine used by the cerebral cortex is produced in situ from thyroxine by a local 5′-deiodinase.[37–40] Thus, low serum thyroxine rather than low serum triiodothyronine indicates poor availability of thyroid hormones for the nervous system. In the animal model a deficiency of thyroid hormones leads to inhibition of cell differentiation and impaired myelination in a short critical age period.[31 33] In 33 very preterm (≤31 weeks) and very low birthweight (≤1500 g) infants, prolonged hypothyroxinaemia was associated with a delay in progression in nerve conduction velocity, especially in those infants who also required ventilation.[41] These results suggest that transient hypothyroxinaemia may interfere with neurological maturation. Furthermore, in our study group low thyroxine values were associated with a delay in psychomotor development not confined to one area of development; a similar type of delay was observed in early treated patients with congenital hypothyroidism.[14–16 18]

As the duration of relevant hypothyroxinaemia may be important, the second measurement of thyroxine (between days 18 and 39, available in 443 infants) was included in an additional analysis. No association with outcome was observed, and neither was the observed association with early thyroxine concentrations changed. Possibly some compensatory mechanisms occur such as observed in the newborn hypothyroid rat[42]: an increased activity of 5′-deiodinase in the cerebral cortex,[37] coincident with a reduction of the rate of degradation of triiodothyronine.[39] These mechanisms act to keep the cerebrocortical content of triiodothyronine at euthyroid concentrations even when serum concentrations of thyroxine are severely reduced.[39] The nervous system in newborn rats is comparable with the nervous system in humans in the third trimester of gestation and it has been suggested that in the hypothyroid human fetus these protective mechanisms may develop.[42] As very preterm infants in the first weeks of life have a similar postconceptional age, the same protective mechanisms may develop in reaction to the reduced thyroxine levels. We are not aware of previous epidemiological studies in which the effect of transient hypothyroxinaemia was studied in a large population of very preterm or very low birthweight children. Lucas *et al* reported that low plasma triiodothyronine (lowest recorded concentration <0·3 nmol/l) in a cohort of 280 infants with birth weight below 1850 g was associated with the risk of developmental disadvantage at 18 months' corrected age.[43] Because in the nervous system hypothyroidism is caused by low serum thyroxine rather than low serum triiodothyronine,[37–40] the reported association of low serum triiodothyronine with delayed development may reflect the underlying effect of low serum thyroxine on the development of the nervous system.

In earlier studies[44 45] such a delay was not observed. However, in one study[43] where the number of infants was very small, thyroxine concentrations were measured in cord blood and development was assessed at a younger age. The thyroid hormone replacement trial[45] compared only five treated children to three non-treated children at 12 months of age, and even fewer at 24 months. In such studies, the detection of a significant relationship is virtually impossible.

Although transient hypothyroxinaemia does not seem to be associated with gross damage, it may contribute to developmental delay. Our findings do not support the view that low thyroxine concentrations in preterm infants are harmless and that these infants do not require replacement treatment. The presumed undesirable effects of thyroid hormone supplementation on metabolism and oxygenation in the first weeks of life should be weighed against the possible benefits in terms of a more favourable developmental outcome at a later age.

We thank all paediatricians in The Netherlands for their participation in this study: the heads of the phenylketonuria and congenital hypothyroidism screening laboratories, the Vaccination Administration Bodies and the Provincial Paediatricians for their enormous help, the National Steering Committees on Phenylketonuria and Congenital Hypothyroidism and the Chief Inspectorate for the State Supervision of Public Health (Dr H P Verbrugge) for giving their consent to this study, Dr J van Rijckevorsel for statistical advice, Dr E A Schlesinger-Was and P H Verkerk for advice and Mrs M Huls-van Vliet for secretarial assistance. The determinations of thyroxine in the second age period were performed by Dr W Schopman (Bergweg Hospital, Rotterdam). The data on the simultaneously determined thyroxine values in filter paper eluates and venous blood samples were provided by Dr J H Kok (neonatologist, Academic Medical Centre, Amsterdam). The data on development were provided by Dr D M van Zeben-Van der Aa (paediatrician, then University Hospital, Leiden)

The study was supported by the Praeventiefonds, The Hague (grant 28–1143).

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Archives of Disease in Childhood 1992; 67: 948–951

Positive rolandic sharp waves in the EEG of the premature newborn: a five year prospective study

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Accepted 12 February 1992

Abstract

In a prospective study of 301 premature newborn infants, neonatal tracings were done to evaluate the use of the electroencephalogram (EEG) and positive rolandic sharp waves (PRSW) in the diagnosis and prognosis of periventricular leucomalacia. Each infant had ultrasonographic studies and standardised neurological examinations at 1 year of age or later. Two hundred and eighty infants were followed up at 1 year.

This study demonstrated that the absence of PRSW was correlated with a favourable motor development (98·2%) and confirmed the great value of PRSW in the diagnosis and the prognosis of periventricular leucomalacia. PRSW were sensitive (98%) and specific (84%) markers of developmental motor disability and were a sensitive (96%) marker of severe spastic diplegia. A frequency above 2/minute was a specific (92%) sign of severe spastic diplegia. Social and language developmental abnormalities were not correlated with the neonatal EEG.

Periventricular leucomalacia and intraventricular haemorrhage are serious neurological complications of prematurity. Numerous studies of infants prospectively scanned with ultrasound have shown that intraventricular haemorrhage had a relatively benign prognosis in the absence of involvement of the brain parenchyma or ventricular dilation[1 2] whereas periventricular leucomalacia had a worse one.[1–3] Though intraventricular haemorrhage is readily recognised by transfontanellar ultrasonography, early positive diagnosis and prognosis of periventricular leucomalacia are not always so easy.

Positive rolandic sharp waves (PRSW) on the electroencephalogram (EEG) were first reported by Cukier *et al* in 1972 in premature newborn infants with intraventricular haemorrhage.[4] We[5] and others[6–8] observed that PRSW were not always associated with intraventricular haemorrhage but rather with white matter necrosis or periventricular leucomalacia. PRSW seemed to be, therefore, a marker of periventricular leucomalacia rather than of intraventricular haemorrhage. From these anecdotal reports we decided to conduct a formal prospective evaluation of the use of the EEG and detection of PRSW in the diagnosis and prognosis of periventricular leucomalacia in premature newborn infants.

Subjects and methods

SUBJECTS

The study was carried out over a five year period between 1 January 1986 and 31 December 1990 on all newborn infants of gestational age less than 33 weeks who were born between 1 January 1986 and 31 December 1989 and admitted to the department of neonatalogy or the intensive care unit of the Centre Hospitalier Universitaire de Rouen; 350 newborns were included. Forty nine died before 3 months and were then excluded from the study. Three hundred and one survived and had at least one EEG within the first 14 days of life; most had two or three EEGs before the age of 1 month.

ELECTROENCEPHALOGRAPHY

Two hundred and fifty five infants had three EEGs. The first EEG was done between days 2 and 4, the second between days 7 and 14, and the third between days 21 and 30. Twenty eight infants had two EEGs and 18 only one. The recordings were done at the infant's bedside and lasted at least 45 minutes. They were performed with a portable 10 or 16 channel machine (Alvar) (six or 10 derivations for EEG, one for an electrocardiogram, one for ocular movements, one for an electromyogram, and one or three for respiratory movements). Bipolar montage was adapted for the newborn infant. The scalp electrodes were put in T4-02, FP2-C4, C4-02, FP1-C3, C3-01, T3-01 in the 10 channel machine montage and in FP2-T4, T4-02, FP2-C4, C4-02, FP1-C3, C3-01, FP1-T3, T3-01 in the 16 channel machine montage. The EEGs were analysed by two of the authors (SM, DP) and another board certified paediatric neurologist. As previously described the PRSW (fig 1) were identified as sharp transients of positive polarity appearing in the rolandic regions (C3-4).[6–9] For each record-

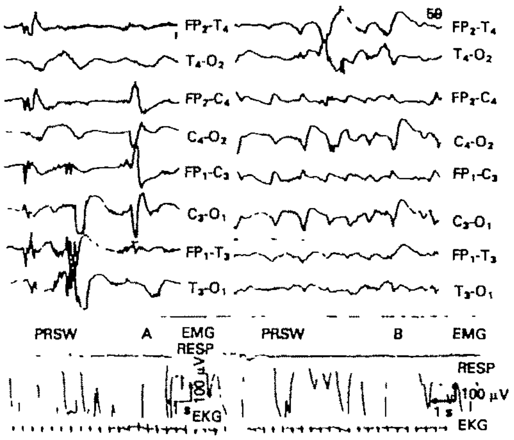

Figure 1 Example of PRSW type A and type B in an EEG made on a 16 channel machine.

ing, PRSW were classified as type A (isolated and sharply differentiated from the background activity) or B (occurring in bundles and less well differentiated from background activity) according to Blume and Dreyfus-Brisac.[10] The frequency (number of PRSW per minute of recording time) was calculated over all the tracing. When it was possible, the persistence of PRSW in two EEGs was noted. Background activity was classified as normal or mildly, moderately, or markedly abnormal, according to the Clancy and Tharp criteria.[9]

ULTRASONOGRAPHIC STUDIES

Each infant had two transfontanellar ultrasonographic studies: one in in the first and another in the third week. They were performed with a real time linear array ultrasound scanner (Sonel 400) with a 5 or 7·5 MHz tranducer. Coronal and sagittal views of brain were obtained. They were seen by a paediatric radiologist without knowledge of the clinical and EEG data. Intraventricular haemorrhage, intraparenchymal haemorrhage, and periventricular cysts in the white matter were studied. Intraventricular haemorrhage was classified as type II when there was no ventricular dilation and type III when there was dilation. Intraparenchymal haemorrhage was considered when there was a unilateral marked echodensity with coexisting intraventricular haemorrhage. Germinal layer haemorrhages were not taken into account and neither were increased parenchymal hypoxic-ischaemic echodensities as infants had only two ultrasonographic studies at a two week interval. In our study, only periventricular cysts were considered as a certain sign of periventricular leucomalacia.

FOLLOW UP

Standardised neurological and developmental examinations were carried out at 3, 6, 9, and 12 months at least and at 24 months in the older infants. They were classified into three motor developmental groups: I: always normal; II: transient or minor motor developmental abnormalities with hand free sitting acquired at 1 year and walking independently acquired at 2 years; and III: severe motor abnormalities with spastic diplegia or quadriplegia. Social and language development was evaluated by Brunet-Lezine tests at 1 and 2 years.[11] It was abnormal below 75, normal above. Because of the duration of follow up standardised measurement of cognitive development was not obtained.

STATISTICS

Different groups were compared by the χ^2 test, with Yates's correction or Fisher's exact test, as appropriate; p values were considered significant below 0·05. When there was a significant difference in comparing groups for one criteria, sensitivity, specificity, predictive positive and negative value, and constant k of relative risk were calculated.

Results

ELECTROENCEPHALOGRAPHIC ANALYSIS

Eight hundred and thirty nine EEGs were analysed. PRSW were observed in 114 of the 301 infants (38%). The first PRSW were seen within the first 14 days in 106 infants (93%). Eighty (70%) had both types A and B in the same recording or in different recordings. Six had only type A and 28 type B. Frequency is shown in fig 2. Persistence of PRSW was noted in two recordings at least in 63/113 (56%) of cases with two or three EEGs and PRSW.

Thirty five (12%) infants had an abnormal background (eight mild, 19 moderate, eight marked). Twenty two of the 35 had an abnormal background and PRSW (eight mild, nine moderate, five marked). In 33 infants an abnormal background was seen in the first EEG. In only two of these 33 did the background abnormality persist in the second recording. Two infants had a moderately abnormal activity only in the second EEG.

ULTRASONOGRAPHIC STUDIES

Twenty one infants (7%) had an intraventricular haemorrhage, eight of the 21 with a dilation (type III). There was no intraparenchymal haemorrhage. Eighteen (6%) had periventricular cysts. Three of the 18 with cysts also had an intraventricular haemorrhage.

OUTCOME

At 1 year of age 21/301 infants were lost to follow up. Two hundred of the 280 had a normal motor development (group I). Eighty were neurologically impaired at follow up: 52 had transient or minor motor abnormalities (group II) and 28 a severe spastic diplegia or quadriplegia (group III).

Prevalence of impaired motor development in infants followed up within the first year was 28·6%. Prevalence of severe diplegia or quadriplegia (group III) was 10%. Developmental quotient for social and language development was low in 20 infants. Three infants had impaired development without spastic diplegia, and 17 had associated diplegia or quadriplegia.

Two hundred and fifteen infants of the 280 were investigated at 2 years. Forty infants were lost to follow up. Forty six did not reach 2 years of age. One hundred and thirty six of the 215 were normal. Of the remainder three had

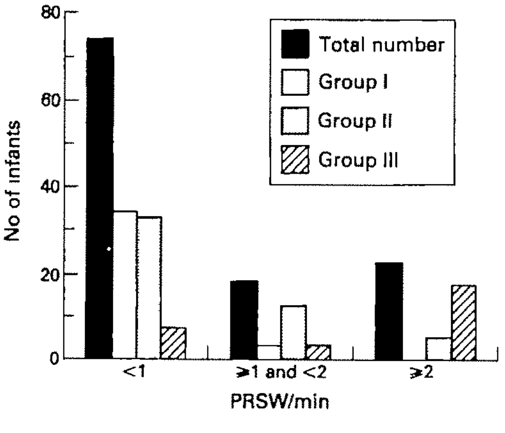

Figure 2 Electroencephalography the first column shows the total number of infants in each PRSW frequency group and the last three columns the distribution of PRSW frequency in each motor development group.

impaired development without motor impairment, 48 belonged to group II, and 28 to group III.

EEG AND ULTRASOUND
PRSW were present in all 18 children with cystic periventricular leucomalacia shown by ultrasound. Thirteen of the 21 (62%) infants with intraventricular haemorrhage (10 type II and three type III) had PRSW. Eighty six of the 114 infants with PRSW had normal ultrasound scans.

EEG AND OUTCOME
The distribution of PRSW in the groups followed up is shown in fig 3. Altogether 98·2% of the infants without PRSW had normal motor development. Sixty eight per cent of the infants with PRSW and only 1·8% of the infants without had impaired motor development. The absence of PRSW was a sensitive and specific sign of right motor development (sensitivity=81%, specificity=96%). The PRSW were very sensitive (98%) and specific (84%) markers of impaired motor outcome (group II plus III) and were sensitive markers of severe motor handicap (96%) (group III) but less specific (65%). An infant with PRSW had 33 times the risk of having a severe spastic diplegia than an infant without PRSW. Thirty seven infants with PRSW had no delay in motor development. Three infants had no PRSW but an abnormal motor development (two a moderate one, one a severe one). The infant with no PRSW and severe diplegia had only two EEGs in neonatal period (one at D2 and one at D24).

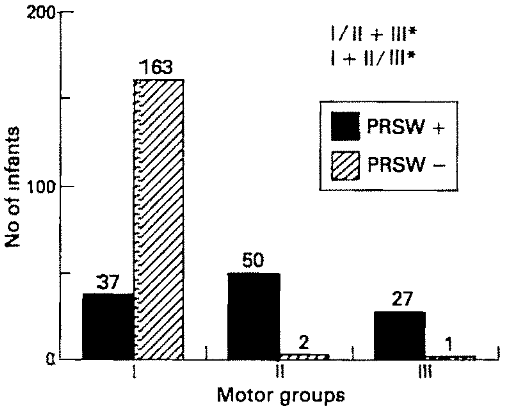

*Figure 3 Electroencephalography in follow up groups showing number of infants with or without PRSW in each motor development group; *p<0·00001*

Frequency above 2/minute was statistically different between group III compared with groups I plus II (p<0·00001) (fig 2). It had a good specificity as a bad prognosis marker (97%) but a low sensitivity (50%). Among the 37 infants with PRSW but normal motor development, PRSW appeared less than 2/minute in all and less than 1/minute in 34 cases. Neither persistence of PRSW nor type A or B were significant prognostic markers.

There was no correlation between abnormal background and language and social development in our study.

EEG, ULTRASOUND, AND OUTCOME
The results are shown in the table. In the infants with impaired motor development (group II and III), PRSW on the neonatal EEG were more frequent than cysts seen on ultrasound. The infants with an intraventricular haemorrhage and PRSW (62%) were in the three motor developmental groups whereas the infants with an intraventricular haemorrhage and without PRSW (38%) were all in the group I.

Discussion

A lot of studies have shown the importance of sequential ultrasound scans in the diagnosis of periventricular leucomalacia.[1-3] [12] Our prospective study confirms the great value of an EEG associated with ultrasound in the diagnosis and the prognosis of periventricular leucomalacia.

In our study the incidence of PRSW (38%) is comparable with that of Lacey *et al* (37%).[13] The absence of PRSW on the neonatal EEG is correlated with unimpaired motor development (98·2%) whereas in their presence impaired development is more frequent (68%). PRSW are a good, sensitive, and specific diagnostic marker of impaired motor outcome. They are a good, sensitive diagnostic marker of severe motor abnormalities (group III) but not a specific one. Such motor abnormalities are known to be due to periventricular leucomalacia.[14] Periventricular leucomalacia can be seen on ultrasound when there is development of cysts. But it is noteworthy that hypoxic-ischaemic parenchymal lesions can be undiagnosed by ultrasound when there is a diffuse gliosis or small areas of periventricular leucomalacia.[15] In our study, 18 of the 80 infants with impaired motor outcome had cysts. Therefore in premature newborns PRSW are a useful sign of neonatal periventricular ischaemia with impaired motor development.

Outcome, PRSW, and lesions seen on ultrasound

Ultrasound appearances	*Group I*		*Group II*		*Group III*	
	PRSW–	*PRSW+*	*PRSW–*	*PRSW+*	*PRSW–*	*PRSW+*
Cysts						
Without	163	37	2	47	1	12
With	0	0	0	3	0	15
Intraventricular haemorrhage:						
Without	155	32	2	46	1	23
With	8	5	0	4	0	4[1]
(type III)	(5)			(1)		(2)

[1] ¼ also had cysts

Some infants have PRSW but no motor sequelae. None of these infants have a high frequency of PRSW (≥2/minute); this is the single most specific marker of severe impaired motor development in our study. These infants will also probably have some neonatal white matter ischaemic lesions. Perhaps they will later have cognitive developmental abnormalities, minimal brain dysfunction, and problems with educational achievement.

PRSW were first reported by Cukier *et al* in premature infants with intraventricular haemorrhage.[4] As reported by Lacey *et al* in their study of infants with intraventricular haemorrhage, some had PRSW and others did not.[13] The infants with PRSW and intraventricular haemorrhage (with or without dilation) have a worse motor development than those without PRSW, who are always normal. In the former case intraventricular haemorrhage is associated with ischaemic parenchymal lesions, which are a more critical determinant of outcome than the amount of haemorrhage in the ventricle.[7] Three of these infants also had evidence of cysts seen on ultrasound.

Unlike other reported findings,[7 13 16] background abnormalities were not a prognostic sign in our study. Marked and persistent background abnormalities are usually bad prognostic markers.[13 16] Several facts can explain the lack of significance in our study. Firstly, it concerned only infants who survived the neonatal period and secondly, the infants were all less than 33 weeks of gestational age. In these immature babies, the cerebral cortex is spared the effects of ischaemia because of its rich leptomeningeal arterial supply.[17] In our study one infant later developed infantile epilepsy and one West's syndrome. Finally, the eight children with marked background EEG abnormalities all had excessive interburst activity lasting for more than a minute. They never persist in two EEGs. Only one infant with marked background abnormalities is impaired for social and language development. Only two infants have persistent, but moderate, background abnormalities; both are normal.

This study demonstrates the need for serial EEGs in the neonatal period in premature newborn infants. They are useful for predicting both favourable and unfavourable outcome.

We thank Dr D Samson-Dollfus for valuable advice and analysis of the EEG, Dr N Moore for valuable editorial comments, Dr J Menard, for statistical analysis of the data, and C Berland for skilful technical assistance

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Archives of Disease in Childhood 1992; 67: 952–955

Occurrence of suppurative lymphadenitis after a change of BCG vaccine

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Abstract

BCG vaccines are the oldest vaccines in use today, but the protective effect of the vaccination is still controversial. The risk of contracting tuberculosis is low compared with the possible complications after this vaccination. In Austria the formerly used BCG vaccine was not available in the required amount and another vaccine was released by the drug authorities. This product, with a more virulent strain, was used between August and December 1990, and this increased the incidence of complications. Eighty four of 1950 vaccinated newborn babies developed severe suppurative lymphadenitis three to 28 weeks after the vaccination, and surgical treatment was found to be necessary. Isoniazid treatment did not prove to be successful when the lymph node exceeded a certain size. Culture was successful in 46% up to week 20; after 20 weeks no culture became positive. All cultured bacteria were isoniazid sensitive.

The question of general vaccination is raised and several points were considered before we came to the conclusion that except for high risk groups a general vaccination programme for neonates is not justified in Western countries.

BCG (Bacille Calmette-Guérin) vaccines are the oldest vaccines in use today. They were derived in 1906 by in vitro attenuation and, after 230 in vitro culture passages by Calmette and Guérin, were first used as oral vaccines in 1921. The subcutaneous application used at the present time was introduced by Wallgren in 1927

After vaccination a positive tine test has been reported in 44% to 84% of cases and an even higher percentage (98%) reported for the Mantoux test two years after vaccination.[1 2] The protective effect of the BCG vaccination has been estimated in many studies to be between 0 and 80%; in infants it seems to lie around 60%, based on known contacts of persons with confirmed tuberculosis.[3–5] Recently the preventive impact of BCG vaccination has been shown by reports of high risks of tuberculosis in infants—in Egypt 76·7% and in Togo 64·5%—who had not been vaccinated.[4 6] The protective effect of vaccination wanes significantly after the age of about 5 years [1 4 7]

In 1952 the Ministry of Health in Austria, as in many other countries except for the USA and the Netherlands, both of which never used it on a national scale, recommended a general vaccination of newborn infants as a preventive measure against tuberculosis. In Germany the vaccination of the newborn was stopped due to complications in 1976. In Austria the risk of contact with tubercular bacilli during infancy is low (the incidence of reported cases in the whole population is less than 0·05%) except in diseased families.[8] Complications with BCG vaccines, such as suppurative lymphadenitis, osteitis, or even generalised tuberculosis, were reported in 0·01–3·8% even with the earlier strain. Nevertheless, in our hospital we had not performed any operation for suppurative lymphadenitis since 1974.[9 10]

Taking into account the low risk of acquiring tuberculosis (0·03%) and the incidence of severe complications from using the vaccine, the recommendation in Austria in 1989 changed to vaccination of high risk groups only: those in slum districts, refugee quarters, or endemic areas, children of diseased families, or of parents working in danger zones such as certain hospitals.[11] Nevertheless, many paediatricians did not change their views and continued with general vaccination.

Based on the false assumption that paediatricians were following the health authorities, recommendation, BCG Berna (strain Kopenhagen) was not stored in a sufficient amount. The vaccine BCG-Pasteur Intradermal P, Charge R 5520, was released by the Austrian drug authorities and the usual demanding licencing procedures were dropped. However, this product contains a much more virulent strain of the tubercle bacillus. It was already known by the World Health Organisation (WHO) to produce a higher rate of complications,[12] and for this reason the vaccine had been replaced. The Pasteur vaccine was used in some hospitals in the dosage of about 0·05 ml intradermally from the beginning of August to December 1990 until its use was prohibited by the Ministry of Health on the 28 November as a result of the alarming reports of a sudden increase in the occurrence of suppurative lymphadenitis.

The known fact led to the conclusion that the new vaccine raised the incidence of complications—a suspicion we initially expressed in a preliminary report.[13]

Subjects and methods

The department of paediatric surgery of the University Hospital Innsbruck is the only centre for paediatric surgery in the Tyrol, an area with about 500 000 inhabitants. In the critical period from August to December 1990, 3386 children were born and 1950 of these were vaccinated with the Pasteur vaccine. This is documented

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Accepted 4 February 1992

by the authorities responsible for public health in the country. The dosage used was 0·05 ml, but in intracutaneous application the real amount is not exactly determined, because a small amount of the vaccine flows back due to the high intracutaneous pressure.

All children in this area were admitted to our hospital if surgical treatment was found necessary. The indication for surgical treatment was a fluctuating lymph node exceeding 1 cm in diameter, the inflammation infiltrating the surrounding skin, or spontaneous perforation or fistula. Under general anaesthesia an excision and excochleation of the necrotic tissue was performed. The material was sent to the Institute for Bacteriology where culture was developed on Löwenstein Jensen agar.[14]

Results

All 1950 newborn babies were mature except for one who was born in the 37th gestational week. The mean (SD) birth weight was 3500 (480) g. From November until 10 June, 84 of these children developed symptoms and were admitted for surgical treatment. The time between vaccination and surgery was surprisingly long. Suppurative lymphadenitis occurred within three to 28 weeks with a mean of 13·8 weeks (fig 1).

At the time they underwent surgery 34·5% of the infants had been on isoniazid treatment for one to 12 weeks already. Localised lymphadenitis was present in 44 boys and 40 girls: its distribution was axillary (59·5%), supraclavicular (29·7%), nuchal (3·6%), cervical (3·6%), scapular (2·4%), and on the upper arm (1·2%). In 92·9% it was unilocular, and 7·1% had more than one enlarged lymph node at a different location. The size ranged from 1 to 4 cm in diameter. The area was typically reddened and in 4·7% spontaneous perforation occurred (figs 2–4). In 92·9% one operation, in 5·9% two, and in 1·2% three repeated operations were necessary due to further occurrence to lymphadenitis in another location.

In these infants the suppurative lymph nodes were totally removed surgically and showed caseous necrosis after incision. The excised necrotic tissue was sent to the Institute for Bacteriology for culture. On Löwenstein Jensen agar cultural detection of tubercle bacilli was successful in 46% up to week 20 after vaccination. After 20 weeks no culture became positive. All cultured bacteria were isoniazid sensitive.

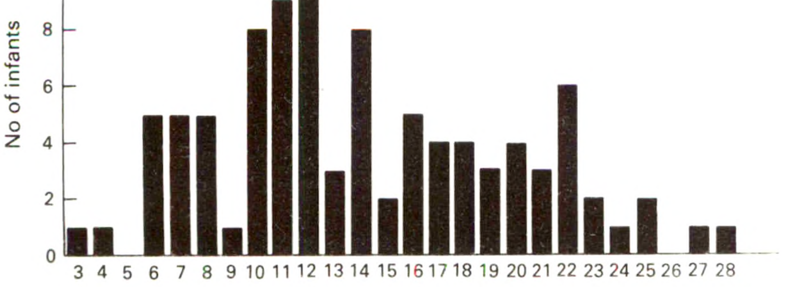

Figure 1 Suppurative lymphadenitis in newborn infants showing the time of surgery in reaction to vaccination (University Hospital Innsbruck).

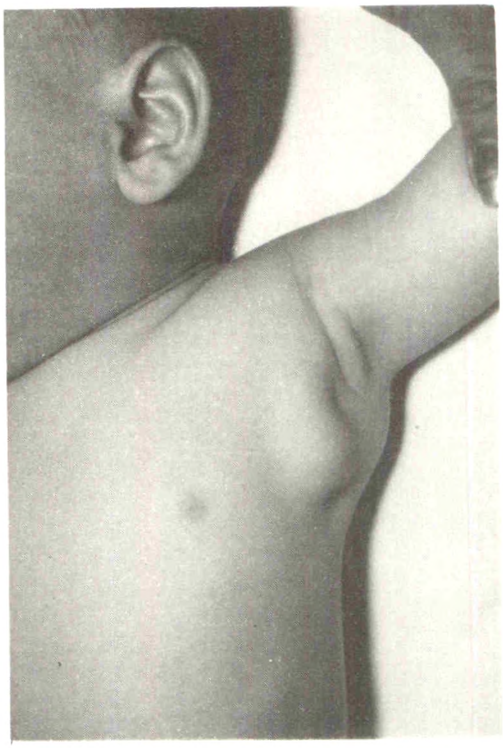

Figure 2 Lymphadenitis 10 weeks after vaccination.

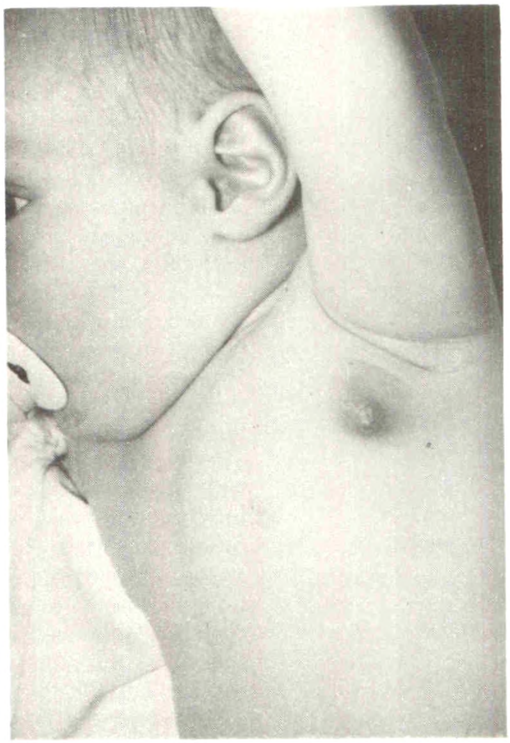

Figure 3 Lymphadenitis 12 weeks after vaccination, with infiltration of the skin.

All children were treated with isoniazid 10 mg/kg body weight plus 10 mg vitamin B 6 (Benadon, Roche) daily for six weeks.

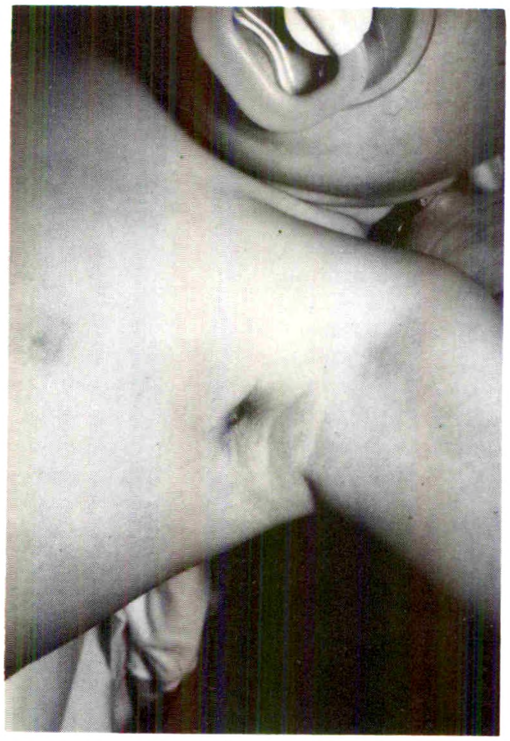

Figure 4 Lymphadenitis 13 weeks after vaccination, with spontaneous perforation.

Discussion

Infection from tuberculosis is rare in neonates and infants, but when it happens it is dangerous and means a prolonged morbidity despite all known therapeutic measures. In principle, a vaccination should solve these problems but a recommendation for general vaccination against tuberculosis needs some consideration.

Firstly, the incidence of tuberculosis has decreased dramatically. This started even before the tubercle bacillus was detected and was due to improvements in social standards and nutrition during the last 100 years. Neither chemotherapy nor vaccination alone have influenced this drop in cases of tuberculosis significantly. Therefore the number of infectious persons with open tuberculosis had declined.[8 11 15 16] Incidence lies now about 0·03% in Western countries.

Secondly, there are complications arising from the use of tubercular vaccines. The rate overall is estimated at about 0·01% to 3·6% comprising suppurative lymphadenitis (1/100), osteitis (1/100 000), and even fatal generalised tuberculosis (1/1 000 000).[2 17–19] Reported complication rates depended on the dosage of vaccine used being 0·68% and 0·09% respectively for 2×10^5 and $0{\cdot}5\times10^5$ viable units of the Pasteur vaccine.[18] In striking contrast is our rate of severe complication with 1×10^5 viable units of this vaccine, making surgical treatment necessary in 4·5%. One report showed the non-suppurative lymphadenitis to occur in 18% of children vaccinated with a Pasteur vaccine.[20]

Thirdly, the protection rate was supposed to be 80% for a duration of about 15 years, an opinion based on positive tine or Mantoux tests. However, there are reports on the waning effectiveness of vaccination after the age of 5 years. Even if in non-vaccinated children the rate of infection is higher than in vaccinated ones it is not acceptable to compare these two groups by randomised studies only without taking the social and nutritional status into account.[15 21] The most reliable report is a case-control study[22] showing a protection rate of 64%.

Fourthly, vaccination means a loss of the diagnostic value of intracutaneous tests (tine, Mantoux), which only show a positive reaction due to vaccination and not to 'wild type' infection.

Statistically, a life span of 100 years carries the same risk of acquiring tuberculosis as of suffering severe side effects due to vaccination. Even with vaccination there is no guarantee of total protection; the possibility of increased resistance has never been confirmed. Furthermore, no positive effect of vaccination in reducing the death rate can be shown; since 1970 no child (0–14 years) living in our area had died from tuberculosis. The tine test of Mantoux test is no proof of protection, it shows only that contact with bacilli has taken place.

After taking all these facts into consideration we must come to the conclusion that a general vaccination programme for neonates lacks justification. The WHO and also the Austrian health authorities met these deliberations with their recommendation to stop general vaccination in neonates except in 'high risk groups'.

In Austria, when the BCG vaccine was replaced by another product, the Pasteur vaccine, which uses a different strain of the bacillus, none of the usual licensing procedures were enforced. Also, each strain of bacillus reacts differently, and these strains cannot be compared directly with each other.[12 20 23] It would appear that neither the producer nor licenser was aware of reports concerning the increased complication rate of the new vaccine. They allowed the production and commercial distribution of the product. This raises the question of the value of control procedures performed by or for a company. Also the actions of the licencing institution in allowing the commercial distribution of the vaccine cause concern.

The site of lymphadenitis in the supraclavicular, nuchal, and even cervical region must be attributed to a wrong application point. Paediatricians seem not to be aware of vaccinating at a point slightly above the recommended location —that is over the insertion of the deltoid muscle.

The complication rate reported by us refers only to severe cases, which were all sent to our centre. The overall complication rate is even higher, as this included cases with less severe lymphadenitis where the conservative approach may have been successful.

Some patients had already had isoniazid treatment before surgery. Although all tubercle bacilli were isoniazid sensitive, the inflammatory process proceeded when the lymph node had reached a certain size. The failure of conservative measures clearly showed that surgical excision is the treatment of choice in fluctuant, enlarged lymph nodes or when they have infiltrated the skin.[24]

The consequences of this occurrence, which raised hysterical reports and discussions in the press and led to a considerable financial burden for Austria, should result in preventive measures to keep the standards of medical services at a high level in the true sense of *primum non nocere*.

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Archives of Disease in Childhood 1992; 67: 956–957

JC virus associated meningoencephalitis in an immunocompetent girl

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Abstract

JC virus is most commonly acquired during childhood, and no clinical illness has been associated with primary infection, which is assumed to be asymptomatic. The only disease associated with JC virus to date is progressive multifocal leucoencephalopathy (PML), which is usually caused by viral reactivation in immunocompromised adults. A chronic meningoencephalitis associated with an active JC virus infection in an immunocompetent 13 year old girl is described.

JC and BK viruses are both members of the polyomavirus subfamily which infect humans. A high proportion of the population has serological evidence of infection, with the peak age of acquisition occurring during childhood. Primary JC virus infection is most common between the ages of 8 and 13 years. After infection, these viruses remain latent in the kidney and are subsequently reactivated during periods of immune dysfunction. It is under such circumstances that polyomavirus infection usually gives rise to symptoms. BK virus is associated with ureteric stenosis and haemorrhagic cystitis in transplant recipients and mild respiratory symptoms have been noted in immunocompetent children suffering primary infection. By contrast, JC virus has only been associated with progressive multifocal leucoencephalopathy (PML), usually among immunosuppressed individuals, particularly those suffering from AIDS.[1] No illness has been associated with primary JC virus infection in the normal host.

PML is characterised by the insidious onset of asymmetrical neurological impairment, due to multifocal demyelination in the brain, which is progressive and usually leads to death within months. The definitive diagnosis of PML is by immunocytochemical and histological examination of brain biopsy material.[1] Serological assessment of blood and cerebrospinal fluid (CSF) is only helpful in a minority of cases, possibly because of the suppressed immune system in these individuals, and also because PML probably represents reactivation rather than a primary JC virus infection.

We now present a case of active JC virus infection associated with an unusual neurological syndrome in a non-immunosuppressed 13 year old girl.

Methods

Total JC antibodies were detected by haemagglutination inhibition and are expressed as a titre. JC IgM was detected in an antibody capture radioimmunoassay similar to one described earlier for BK virus.[2] Full details of this assay are to be published shortly. Sera are deemed to contain significant IgM if the ratio of test sample result to negative control value (T:N) is >5.

Case report

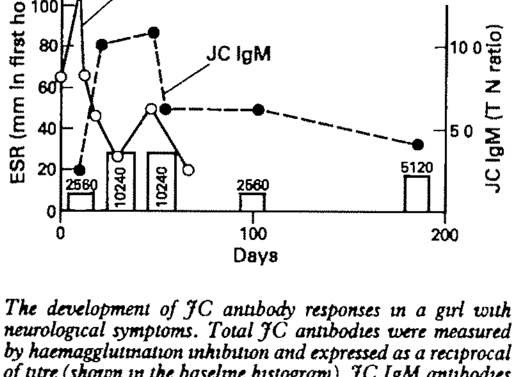
A 13 year old girl presented to our casualty department in late October after tripping over her shoe lace and sustaining a head injury. This was associated with a brief episode of loss of consciousness. Initial examination and a skull *x* ray film were normal and she was discharged home well. She returned one week later with a history of headaches, vomiting, and aggressive behaviour. The behavioural changes had been developing over two to three weeks before the head injury. She had also lost 3·2 kg in weight over the same period.

On examination she had a flat affect but there were no abnormal neurological findings. Her tongue was fissured and her lips were cracked but the rest of the systemic examination was normal. She was observed on the ward where her illness progressed. Six days after her admission she suffered her first recorded pyrexia and this was associated with retention of urine which required urethral catheterisation. Investigations at this time showed her to have a neutrophil leucocytosis and a raised erythrocyte sedimentation rate (ESR) but her urine and blood cultures did not grow any microorganisms. Other investigations included an abdominal ultrasound, a drug screen, and a pregnancy test, all of which were normal or negative. The patient continued to deteriorate with a flaccid paraplegia of the lower limbs, associated with extensor plantar responses. There was incontinence of urine and faeces and anaesthesia of saddle area distribution, as well as paraesthesia below the level of L2. In the upper limbs there was a mild bilateral lower motor neurone weakness with maintained palm reflexes and no sensory impairment.

A lumbar puncture was abnormal with a raised CSF pressure (300 mm H_2O), slightly high protein (0·5 g/l), and total white blood cell count of 75×10^6/l (70% mononuclear). CSF electrophoresis showed an inflammatory leak pattern with acute phase proteins but no oligoclonal bands. Electroencephalograms were abnormal on multiple occasions, showing bilateral delta waves and intermittent high amplitude slow waves of 3–4 cycles/second, mainly right sided, but with no epileptic features. These appearances were compatible with an encephalopathic type illness. Computed tomography and magnetic resonance imaging scans of the brain and spine were normal. A clinical diagnosis of meningoencephalomyelitis was made.

Serological tests over this period showed the absence of serum IgG antibodies to cytomegalovirus, herpes simplex virus, and Epstein–Barr virus, and no change in titres of serum antibodies to influenza A and B, varicella zoster virus, and measles. Rubella IgG antibodies were present in her serum but were not detectable in CSF. A very low level of CSF measles antibodies was detected, but this was compatible with an inflammatory leak. No viruses were grown from successive cultures of saliva, stool, urine, and CSF, thereby excluding infection with mumps or an enterovirus. JC virus culture is a difficult procedure, requiring primary brain tissue, often taking up to one year, with a low pickup rate. It was therefore not undertaken. The JC virus serology is represented graphically (figure). The titre of total antibodies (haemagglutination inhibition antibodies) showed a fourfold rise, up to 1/10 240, and there was also a rise in the concentration of IgM, corresponding with the onset of febrile illness, which was preceded by a prodromal illness. A low titre of CSF JC virus antibody was detectable, but this can be attributed to a leak of protein from serum during the inflammatory process. The ESR mirrored the severity of symptoms.

The patient's acute symptoms resolved seven weeks after hospital admission and she was discharged. Her clinical course has fluctuated over the five month period since then with episodes of neurological relapse (see below). She showed some clinical features of PML, including persistent impairment of cognitive function, and disturbance of speech, vision, and movement. However, the typical rapid deterioration did not occur and she has made a neurological recovery, although some variable impairment of concentration and learning abilities persist. JCV IgM concentrations fell over time and, although there is a twofold increase in haemagglutination inhibition antibody titre with the most recent serum sample, this change is within the limits of assay variation.



The development of JC antibody responses in a girl with neurological symptoms. Total JC antibodies were measured by haemagglutination inhibition and expressed as a reciprocal of titre (shown in the baseline histogram) JC IgM antibodies were expressed as a T:N ratio

Our patient had no impairment of cell mediated or humoral immunity as shown by normal serum immunoglobulins, T cell count, and subsets which were all measured at the recovery stage of her illness. She was also screened for evidence of sarcoid, human immunodeficiency virus, lymphoproliferative disease, tuberculosis, systemic lupus, and diabetes and all tests were reported as normal or negative.

Discussion

A brain biopsy for histological diagnosis was not undertaken but it is possible that this girl suffered a mild form of PML. Primary JC virus infection has been associated with PML, albeit in an immunosuppressed child,[2] and a non-progressive form of PML has been documented in adults.[3 4] On the other hand, a febrile illness, as observed in our patient, does not occur in PML, and computed tomography and magnetic resonance, both sensitive methods for detection of the demyelinating brain lesions,[5] were normal in this case. It is therefore likely that she suffered a chronic meningoencephalitis rather than classical PML. Of particular interest was the relapsing nature of her illness and the fact that behavioural problems remained, some seven months after onset, despite the resolution of all other neurological abnormalities. In fact her personality change predated other symptoms, leading to a major psychiatric input into her care during the initial stages of her illness.

This could be a primary JC infection, although no stored serum existed from before onset of symptoms so a seroconversion could not be documented. We have previously shown that of 46 children with rashes, none developed a serum concentration of JC IgM approaching that detected in this case (unpublished results). Further, a rising titre of IgG and IgM was observed over the period of this girl's illness. These two observations support our thesis that the serological findings we report are specific, and compatible with active JC virus infection. Interpretations other than a primary infection are that her illness is an atypical PML in a girl with a subtle lack of immunocompetence, or that the meningoencephalopathy is unrelated to JC virus infection and the immune response detected represents a reactivation of JC virus after the clinical illness. It is interesting to speculate that JC virus can cause forms of neurological illness other than PML. The availability of a JC IgM assay, utilised in this case, should help to investigate this possibility in children with otherwise unexplained neurological symptoms.

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Archives of Disease in Childhood 1992; 67: 958–959

Necrobacillosis with pancytopenia

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Abstract

Two young children whose presentation with necrobacillosis caused considerable diagnostic difficulty resulting in referral to an oncology unit are described. In both cases their severe suppurative multisystem illness was complicated by pancytopenia. One had bone marrow infarcts and severe endocarditis in addition to pulmonary involvement and the other had osteitis which resulted in a deformed humerus.

Necrobacillosis, the septicaemic illness caused by *Fusobacterium necrophorum* was first described as a uniformly fatal illness by Lemierre in 1936.[1] It is a severe feverish illness particularly affecting previously healthy young adults who classically develop multisystem abscesses with predominant pulmonary involvement after initial sore throat. Other manifestations involving the upper respiratory tract, and apparently isolated metastatic infection can occur.[2] Staphylococcal infection is often considered.[3] However, it remains unknown to many clinicians and has been described only rarely in children. We have recently seen two children with differing features of this condition, but both had haematological involvement and have been left with significant long term morbidity.

Case reports

CASE 1

A previously healthy 2 year old boy was referred to his local hospital with a two month history of lethargy, anorexia, and weight loss with progressive fever, cough, and pallor. He had fever with minimal left sided consolidation on a chest *x* ray film for which he was treated with intravenous penicillin and flucloxacillin. Haematological investigation showed a haemoglobin concentration of 31 g/l, mean corpuscular volume 68 fl, white cell count 12×10^9/l with 54% neutrophils, and platelet count 71×10^9/l. The blood film showed anisocytosis with teardrop poikilocytosis. Insufficient blood was obtained to measure the serum ferritin concentration. Serum B12 and folate were normal. The patient was transfused and then was referred with suspected disseminated malignancy. Bone marrow examination revealed gross myeloid hyperplasia with the neutrophils showing severe toxic changes. There was depressed erythropoiesis and virtually no stainable iron was found. Several large areas of necrosis were present in the marrow biopsy specimen. There was no evidence of malignancy and the appearances were suggestive of a severe toxic insult.

Intravenous azlocillin and gentamicin were commenced, but after 72 hours of continued fever were changed to vancomycin and ceftazidime, to which metronidazole was added when an anaerobe was reported on the original blood culture. Purulent fluid drained from both a right pyopneumothorax and a chest wall abscess was sterile. On day 6, the anaerobe was confirmed as *F necrophorum* sensitive to metronidazole and penicillin to which he was changed. He had a respiratory arrest associated with the development of a right pneumothorax and worsening right sided consolidation. He was admitted to intensive care for ventilation where his course was complicated by bilateral pneumatocoeles that resolved slowly. He had two seizures, but no evidence of cerebral abscess was found. A new ejection systolic murmur was noted at the apex, but no structural lesion was evident on cross sectional echocardiography. He was successfully extubated after two weeks and antibiotic treatment was continued for a further week. Before discharge the peripheral blood count, including mean corpuscular volume, was within normal limits and no evidence of immune deficiency was found. Two months later he was admitted in acute cardiac failure secondary to severe mitral incompetence, which was thought to be due to endocarditis occurring during the original illness. He remains well after mitral valve replacement.

CASE 2

A 5 year old girl was admitted to her local hospital with a one week history of malaise, fever, and diarrhoea for which she had been treated with amoxycillin. On examination she was feverish and looked pale and a diagnosis of haemolytic uraemic syndrome was suspected. Haematological investigation showed a haemoglobin concentration of 78 g/l, mean corpuscular volume 77·3 fl, white cell count 19×10^9/l with 86% neutrophils, and platelet count 47×10^9/l. Her electrolytes and creatinine were normal and there was no red cell fragmentation. The anaemia and thrombocytopenia were thought to be consistent with toxic marrow depression. Intravenous chloramphenicol, cefuroxime, and ampicillin were commenced but she remained feverish. On day 6 a painless swelling developed in her left mastoid region and pus drained from her left ear. A left cortical mostoidectomy and drainage of a Bezold's abscess was performed. At the same time *F necrophorum* was isolated from her original blood culture and treatment with penicillin, metronidazole, and ceftazidime was commenced.

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Accepted 26 February 1992

Despite appropriate antibiotics she remained unwell and feverish for a further two weeks. During this time radiological investigations, including a bone scan and computed tomogram, failed to show further abscesses. She deteriorated and developed rigors, bone pain, headache, irritability, and photophobia. The white blood cell count was now $2{\cdot}4\times10^9$/l, with a neutrophil count of $1{\cdot}4\times10^9$/l, although her platelet count was improving. She was referred for exclusion of underlying immunodeficiency or malignancy. The clinical features were felt to be compatible with disseminated necrobacillosis, and she was reinvestigated for the presence of metastatic abscesses. Antibiotic treatment was changed to penicillin, metronidazole, and imipenem. Despite the lack of clinical signs and symptoms radiological studies revealed severe active osteitis of the right humerus with mild osteitis on the left. However, no evidence of cerebral abscess was found. Bone marrow examination was normal.

After six weeks in hospital, her temperature settled and her full blood count returned to normal. She was discharged home to complete eight weeks of antibiotics. Clinically she made a good recovery, although osteitis has led to a severe deformity of the right arm which may require surgical correction.

Discussion

Many of the commonly described clinical features of this syndrome were seen in our patients: severe protracted feverish illness with rigors, metastatic abscesses, initial diagnostic difficulty with frequent changes of antibiotic treatment, and a slow clinical response.[3 4] However, haematological abnormalities, apart from leucocytosis, have been thought not to occur in necrobacillosis,[5] although patients with a severe infection may have anaemia.[1] Neither pancytopenia, which occurred in both patients, nor bone marrow necrosis which occurred in one, have previously been described in this disease. It is possible that underlying iron deficiency contributed to the severity of the anaemia in case 1.

Review of the literature on necrobacillosis is complicated by frequent changes in nomenclature of the organism. This disease classically occurs after a sore throat, although a primary focus of infection is not always evident. It is unknown why this normal oral commensal becomes invasive. Otitis media and mastoiditis are common presenting features in infants, but rare in adults, and may be associated with central nervous infection in any age group.[2] Septic thrombophlebitis and metastatic abscess formation commonly result in pneumonia and empyema. Bone or joint infection as well as hepatic and renal involvement are frequently found.[1] Bacterial endocarditis has been reported as a rare complication in adults with necrobacillosis. Acute endocarditis of previously healthy valves has been described.[6] The need for mitral valve replacement is more unusual.

F necrophorum has a typical appearance on microscopy but may be mistaken for bacteroides. It can be difficult to culture and requires strict anaerobic conditions.[3] Although the organism is sensitive to many antibiotics, in vitro sensitivity does not correlate well with the clinical response, which is characteristically slow. It is widely suggested that metronidazole is the drug of choice, and that penicillin should be added for a microaerophilic streptococcus which may be grown concurrently.[2] The optimal duration of antibiotic therapy is unknown.

This report highlights the need to consider anaerobic infection, including necrobacillosis, in previously healthy children who develop severe suppurative infection. The early institution of appropriate antibiotics and awareness of the associated complications may help to reduce the morbidity of this rare but serious illness.

The authors are grateful to a multidisciplinary team of paediatricians, paediatric oncologists, microbiologists, intensive care unit staff, cardiologists, orthopaedic surgeons, radiologists, haematologists and nurses, who were involved in the management of these children ME was financially supported by the North of England Children's Cancer Research Fund

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Archives of Disease in Childhood 1992; 67: 960–961

Protein S deficiency: early presentation and pulmonary hypertension

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Abstract

Protein S deficiency usually presents in adults with recurrent or unexplained thrombosis and is thought to have autosomal dominant inheritance. We describe the case of a 5 year old girl with pulmonary hypertension but no evidence of venous thrombosis until postmortem examination. Her parents were first cousins. This potentially treatable condition should be sought in children and their relatives screened.

Protein S is a vitamin K dependent plasma protein which inhibits blood clotting by acting as a cofactor for protein C which in turn inhibits the clotting cascade at the levels of factor V and factor VIII. Protein S exists in two forms in the plasma: free (active) or bound to plasma protein (inactive). It is very rare for symptoms to occur in childhood. We report the case of a 5 year old girl who was referred for assessment of pulmonary hypertension and the diagnosis of protein S deficiency became apparent after she died suddenly.

Case history

A 5 year old girl presented to her local hospital with a five week history of breathlessness, general lassitude, and cyanosis. Her parents were first cousins and there was no family history of cardiopulmonary problems. At 1 month of age she had had a patent arterial duct ligated. She had made an uneventful recovery from this and had been discharged from the cardiology clinic at the age of 6 months.

On admission at the age of 5 years she was centrally cyanosed, with oxygen saturations of about 75% in room air; she showed only slight improvement on 100% oxygen. She had clinical evidence of pulmonary hypertension with no obvious murmurs. A chest radiograph showed cardiomegaly and the electrocardiogram demonstrated right ventricular hypertrophy. Cross sectional echocardiography demonstrated gross right atrial and right ventricular enlargement and marked tricuspid regurgitation. There was moderate global impairment of left ventricular function and a mass in the ventricular apex which was thought to represent a clot, but the differential diagnosis at that stage included a tumour. Ultrasound of the abdomen was normal.

She was anticoagulated and received 3 mg of warfarin on two consecutive days and then heparinised (10 000 units/day). A ventilation perfusion scan was highly suggestive of chronic pulmonary embolism with multiple perfusion defects bilaterally. Cardiac catheterisation was preceded by an inferior venacavogram which showed no obvious clot. Pulmonary hypertension was confirmed (total pulmonary vascular resistance=26·6 units/m^2) at the cardiac catheter and there was no significant response to 100% oxygen. A pulmonary angiogram confirmed perfusion defects in the lung with small distal vessels. Even though the evidence was somewhat conflicting, it was felt in the absence of evidence of peripheral venous thrombosis the most likely diagnosis was primary pulmonary hypertension. However, in view of the possible thrombus in the left ventricle she was maintained on heparin. She was considered for heart-lung transplantation but on her 15th day in hospital she had a cardiac arrest from which she could not be resuscitated.

At necropsy, antemortem thrombus was found in the left and right ventricles and inferior vena cava. There was no active inflammatory infiltrate or evidence of structural abnormality in the inferior vena cava. The pulmonary artery was atheromatous. Patchy areas of infarction were found in the lower lobes of both lungs and the right middle lobe. There was no recent infarction. Histological examination of the lungs showed extensive fibrin thrombus within the pulmonary arteries associated with infarction of distal tissue in all lobes of the lung. There was no histological evidence of vasculiltis affecting the lung.

Haematological results from antemortem blood were only then available and were (range): protein C (immunological) 60% (55–123), antithrombin III 73% (80–120), and protein S (total) 6% (60–120). The protein S concentration was measured eight days after the second dose of warfarin and the international normalised ratio was 1. An enzyme immunoassay (asserachromproteine S, Diagnostica Stago) was used to measure protein S. Her immediate family were screened and the protein S concentrations were normal. There was no family history on detailed retrospective questioning of venous or arterial thrombosis.

Discussion

Protein S is a vitamin K dependent natural anticoagulant that acts as a cofactor for protein C in inactivating the procoagulants factor V and factor VIII. Protein S deficiency was linked to thrombus formation in 1984.[1] Two types of deficiency are described. In type I there is little free protein S, although there is a significant amount bound to plasma protein. Type II is characterised by reduction of both the bound

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Accepted 10 March 1992

and free forms. It is usually described as an autosomal dominant condition and the gene has been assigned to chromosome 3. There is evidence to suggest that two genes for protein S are present within the human genome.[2] A Japanese paper reported several cases of severe protein S deficiency in consanguinous members of a large pedigree.[3] In our patient the parents were first cousins. These reports may suggest autosomal recessive inheritance and the genetics of the disorder require clarification.

The profoundly low protein S concentration cannot be attributed to warfarin. The blood sample was taken eight days after the last dose of warfarin and it is known that warfarin tends to depress protein C concentrations more than protein S,[4] the reverse occurring in our case.

Individuals with low protein S concentrations may not develop thrombosis and therefore other, as yet undefined, factors are important in the clinical significance of deficiency. There are few reports in the literature of thrombosis presenting at less than 15 years of age[4–7] and to the best of our knowledge this is the first case where the child died from the thrombosis. We cannot explain why this girl presented so young with such severe pulmonary hypertension as the absolute concentration does not appear to correspond to clinical severity.[4]

A feature of protein S deficiency is the tendency to arterial thrombosis.[4 7] The patient under discussion had a clot evident in the left ventricle and we would now suggest that a patient of whatever age with unexplained pulmonary hypertension and evidence of arterial thrombus should be considered as having protein S deficiency until proved otherwise. This case highlights the fact that protein S deficiency may present and be lethal in young children. The diagnosis has treatment and possible genetic implications and it is therefore important that it should not be missed. Protein S concentrations should be checked routinely in children and adults presenting with unexplained thrombosis and in patients diagnosed as having primary pulmonary hypertension, as thrombosis may not be obvious clinically. One should be particularly vigilant if there is associated arterial thrombosis.

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Archives of Disease in Childhood 1992; 67: 962–966

CURRENT TOPICS

Myelodysplastic syndromes

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Myelodysplasia is one of the Cinderella subjects of paediatric haematology and oncology. Although cases are rare and probably do not account for more than 3% of haematological malignancies, patients presenting with these disorders pose a very serious challenge to successful diagnosis and management with which we are only just coming to grips. In fact, such is the previous state of confusion that we have no idea of the prevalence of the component disorders and there is little doubt that under diagnosis was itself prevalent. The first tentative steps have now been taken out of the darkness and probable cures are being achieved in previously almost uniformly fatal conditions. The first moves in the right direction were achieved by abandoning the paediatricians inherent love of syndromes and concentrating, with our adult haematology colleagues, on getting some sense and science into classification of the disorders.

Classification

The basic concept of myelodysplasia is a very simple one: the bone marrow is active but ineffective. Thus, there are functional morphological abnormalities and/or pancytopenia. The syndromes thus include the disorders previously called refractory anaemia, smouldering leukaemia, and preleukaemia all of which had a strong predilection to progress to acute myeloid leukaemia at varying pace. One series of childhood acute myeloid leukaemia has suggested that 17% of cases had a preleukaemic phase.[1]

The French-American-British cooperative morphology group has led the way in providing the systematic groundwork for a classification system.[2] Subsequently the Morphologic, Immunologic and Cytogenetic Cooperative Study Group has provided additional cytogenetic information which has allowed further refinement.[3] The conventional approach has been to distinguish myeloproliferative disorders (such as chronic granulocytic leukaemia, essential thrombocythaemia, myelofibrosis, and polycythaemia) from myelodysplasia. This is a somewhat artificial distinction, bearing in mind that all are clonal proliferations and all may evolve to a frank acute leukaemia. However, it forms the basis for the best attempts at classification currently available for childhood myelodysplasia[4] (see table 1) and eventually a better classification will hopefully come out in the biological wash. This includes the two commonest syndromes described in the paediatric literature, juvenile chronic myeloid leukaemia (JCML) and infantile monosomy 7 syndrome. Both of these disorders will presumably take their place under more appropriate headings when more systematic studies are completed, for example, JCML shows some features akin to a well described adult counterpart, chronic myelomonocytic leukaemia (CMML). Table 2 shows a recommended list of investigations required for the diagnosis and classification of myelodysplasia.

I would like to expend a little space on the specific features of the disorders listed in table 1. However, there is insufficient space to deal adequately with chronic myeloid leukaemia, which has been extensively reviewed elsewhere.[5–10] Essential thrombocythaemia and polycythaemia are excessively rare in childhood and the few authenticated cases have also been reviewed elsewhere.[11–13] Malignant myelofibrosis as seen in adults[14 15] is not seen in children and modern techniques have shown

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Table 1 Classification of paediatric myelodysplasia

- Primary myelodysplasia:
  - Juvenile chronic myeloid leukaemia
  - Infantile monosomy 7 syndrome
  - Refractory anaemia
  - Refractory anaemia with excess of blasts
  - Refractory anaemia with excess of blasts in transformation
- Proliferative myelodysplasia.
  - Down's syndrome leukaemoid reactions
  - Myelodysplasia with eosinophilia
  - Philadelphia positive chronic myeloid leukaemia
  - Atypical chronic myeloid leukaemia
  - Familial myelodysplasia
  - Essential thrombocythaemia
  - Polycythaemia rubra vera
- Secondary myelodysplasia:
  - Familial
  - Therapy induced

Adapted from Chessells[4]

Table 2 Investigation of myelodysplasia

- Blood.
  - Haemoglobin+red cell indices
  - White cell count+differential
  - Blood film
  - Fetal haemoglobin concentration
  - Immunoglobulins
- Bone marrow.
  - Aspirate+trephine biopsy
  - Cytochemistry and iron stain
  - Cytogenetics
- Additional tests.
  - Neutrophil function
  - Platelet function
  - Lymphocyte subsets
  - Tissue culture marrow colony assays
  - Antinuclear antibodies
  - Fetal globin glycine:alanine ratio }
  - I:i red cell antigen ratio } Juvenile chronic myeloid leukaemia
  - Carbonic anhydrase }

Adapated from Chessells[4]

that primary myelofibrosis is in fact acute megakaryoblastic leukaemia wherein the proliferating megakaryocytes induce extensive marrow fibrosis.[16]

Juvenile chronic myeloid leukaemia

JCML does appear to be a distinct disease entity, the pathognomonic feature of which is a reversion to a truly fetal haemopoiesis with raised concentrations of fetal haemoglobin above 10%,[17] a fetal pattern of red cell enzymes,[18] and in one reported case the persistence of epsilon globin chains that normally disappear by 3 months of age.[19] The disorder appears to be more common in boys, and children with neurofibromatosis show a higher number of cases than expected of JCML and chronic myeloid leukaemia.[20 21] The usual clinical presentation is with pallor, splenomegaly, and bleeding due to thrombocytopenia. The latter (along with the higher fetal haemoglobin concentration) distinguishes this disorder from monosomy 7 myelodysplasia (see below).[17] Cutaneous xanthomata occasionally occur[20] and led to the outdated description of 'xantholeukaemia'. There is often a facial rash in a butterfly distribution that may also involve the trunk, predate the other findings, and lead to a misdiagnosis of lupus erythematosus, especially as antinuclear antibodies may be present.[22]

Since the original reports of this disorder[23] it has become standard practice to compare and contrast this disorder with Philadelphia chromosome positive chronic myeloid leukaemia. This is a largely pointless exercise and in fact the morphological and some other features, for example the immune disturbance,[22] are more akin to CMML as previously described in adults. Further evidence is provided by the presence of monocyte specific antigens on the surface of mononuclear cells[23] and outgrowth of macrophage colonies in tissue culture.[24] However, the bone marrow may show various cytogenetic abnormalities or be normal and thus there are no diagnostic cytogenetic findings.[25] This is in contrast to monosomy 7 myelodysplasia which can otherwise be indistinguishable,[26] although JCML is more frequently associated with a lower platelet count as well as the raised fetal haemoglobin.[27] As with many of the myelodysplastic disorders in childhood, more can be gleaned from an examination of the blood film than the bone marrow aspirate. The white cell count is usually only moderately raised and rarely above $50\times10^9/l$, anaemia is common, the platelet count reduced, and there is usually a prominent monocytosis often associated with dysplastic granulocytes and some blast cells. The bone marrow findings are similar but usually much less noticeable. The prognosis is very poor and over the last 20 years we have seen 14 children at Great Ormond Street, 11 boys and three girls with a median age of 3 years and median survival of only six months. These patients did not develop a terminal leukaemic 'blast crisis' as is sometimes described, but developed progressive weight loss, nodal enlargement, and some increase in blasts and normoblasts.

Monosomy 7 myelodysplasia

Monosomy and partial deletion of chromosome 7 is found in primary myelodysplasia as described here, but also in *de novo* acute myeloid leukaemia, secondary myelodysplasia, and secondary acute myeloid leukaemia. In each of these disorders there is a defect in neutrophil chemotaxis and killing leading to a particular susceptibility to bacterial infection.[28] The presence of the deletion in biphenotypic leukaemias adds weight to the proposition that monosomy 7 is associated with transformation of a common lymphoid-myeloid progenitor cell.[29] The variability of clinical features in association with abnormalities of chromosome 7 are well illustrated by the experience at this hospital over the last 20 years. During this period we have seen four cases of *de novo* acute myeloid leukaemia, one of secondary acute myeloid leukaemia, one of myelofibrosis with myelodysplasia, one of refractory anaemia with excess of blasts with transformation (RAEB-t), and 13 children with the myeloproliferative syndrome. It is important to note that there are families with an apparent predilection to the development of acute myeloid leukaemia or myelodysplasia and this may be associated with chromosome 7 abnormalities.[30] The 13 children we have looked after with monosomy 7 myelodysplasia presented at a median age of 10 months but the oldest was aged 8 years and had an indolent process of recurrent infections, hypogammaglobulinaemia, and monocytosis over a six year period. Three of the 13 developed acute myeloid leukaemia and one developed massive splenomegaly and marrow fibrosis. The time to the development of acute myeloid leukaemia varied from three months to two years. A third of the cases survived more than two years and thus this disorder is associated with longer survival than JCML with a predilection to the development of acute myeloid leukaemia.

Other myelodysplasias: primary

The current lack of knowledge does not allow a calculation of the prevalence of these disorders. Several series have highlighted the paucity of children who present with the types of myelodysplasia associated with a better prognosis, that is refractory anaemia (RA) and refractory anaemia with ringed sideroblasts (RARS).[31 32] We have seen only two cases of RARS, both of which followed a chronic course. Thus, the vast majority of children with myelodysplasia unfortunately fall into the bad risk categories of RAEB with or without transformation towards acute myeloid leukaemia. All series consistently show a less than 20% chance of survival to five years and there are very few long term survivors. However, there are encouraging reports demonstrating a survival of up to 50% after bone marrow transplantation for those who have a histocompatible sibling.[33] Attempts have been made to identify features associated with prognosis in adults. Features predictive of long survival include pancytopenia, more than 5% blasts in the blood, abnormal localisation of immature precursors on a trephine biopsy specimen, and a karyotype showing complex chromosomal abnormalities.[34]

It has been known for many years that children with Down's syndrome are at risk of a neonatal myeloproliferative syndrome resembling acute leukaemia, which usually undergoes spontaneous remission. Some of these children later develop acute leukaemia after an interval ranging from six months to three years.[35] In addition, children with Down's syndrome and acute myeloid leukaemia can have a prodromal myelodysplastic phase lasting several months with occasional blasts seen on the blood film. There is an obvious need to follow up a series of babies with Down's syndrome in order to determine the true incidence of this transient abnormal myelopoiesis and the risk of development of acute leukaemia. Clinically the disorder resembles congenital leukaemia with hepatosplenomegaly but without the skin infiltration seen in the former.[36] There is a blood leukocytosis with many blast cells, which have recently been shown to be megakaryoblasts.[37] Although these children may develop hyperviscosity problems due to the high white blood cell count, they do not develop severe bone marrow failure although they may need some red cell and platelet transfusions. The management is conservative with supportive care only and the most important thing is to follow up the patients carefully in case they develop acute myeloid leukaemia.

A number of children have presented with hepatosplenomegaly, dramatic eosinophilia, myelodysplasia, and cytogenetic abnormality involving the area of chromosome 5q31 that contains the gene for interleukin-5 (IL-5 'eosinopoietin').[38] We have a patient in whom there is a prolonged history of a severe infiltrative skin disorder and dramatic eosinophilia.

There is a 'ragbag' of other very rare myeloproliferative disorders in childhood. Several have been shown to involve translocations of chromosome 11p15.[39] Rarely, cases otherwise identical to chronic myeloid leukaemia but without the Philadelphia chromosome and with no bcr-abl gene rearrangement[34] are seen in childhood. A morphological review of childhood cases is required and it is possible that they will be classified with CMML. The prognosis of this disorder is said to be poor.

Other myelodysplasias: secondary

Children with congenital bone marrow disorders such as Fanconi's anaemia and Shwachman's syndrome can present with or develop myelodysplasia as well as acute myeloid leukaemia.[40 41] Unfortunately we are also seeing an increased incidence of acute myeloid leukaemia and myelodysplasia in patients treated for malignant disease, most commonly Hodgkin's disease but also non-Hodgkin's lymphoma and other solid tumours. The alkylating agents are most clearly implicated in this susceptibility.[42] The risk of secondary leukaemia and myelodysplasia after treatment for acute lymphoblastic leukaemia is not clear but so far there have only been a few cases reported in the UK.

Cytogenetic abnormalities are found in almost all children with secondary myelodysplasia/acute myeloid leukaemia and are frequently multiple, the majority involving chromosomes 5 and 7 with 3 and 17 being less frequently involved. The chromosome 5 abnormalities always involve 5q23–32, a region containing the genes for several growth factors and their receptors.[43]

Clearly the most important point to be made here is that the planning of treatment for malignant disease should take into account the need to try to avoid the use of alkylating agents where alternative treatments are possible and especially to try to avoid their concomitant use with radiotherapy. This has proved possible with regimens for low grade non-Hodgkin's lymphoma. The published results of treatment for secondary myelodysplasia make depressing reading. Patients with chromosome 5 abnormalities did particularly badly in the past. Remission duration, if achieved at all, tends to be extremely short in this whole group of children before the era of bone marrow transplantation.[42]

Biology of myelodysplasia

Various modern techniques have demonstrated that the myelodysplasias are clonal disorders arising in a multipotent or pluripotent stem cell,[44] and the blood cells produced often survive for a short time and have abnormal function. Disease progression is a function of the expansion of the abnormal clone with progressively abnormal blood count and/or development of acute myeloid leukaemia. This process is frequently associated with immunological abnormalities including raised immunoglobulins, reduced numbers of natural killer cells, and an abnormal helper:suppressor T cell ratio.[45] A variety of abnormalities of bone marrow growth in colony cultures has been described. In children one of the commonest phenomena is spontaneous growth of colony forming unit—granulocyte/macrophage and other patients show reduced growth of multipotent progenitor cells.[26]

A large number of attempts have been made to identify factors associated with disease progression towards acute myeloid leukaemia. One promising line of inquiry relates to the *ras* group of genes which are involved in the regulation of cell proliferation. Preliminary studies have in fact shown that these genes are activated in patients with myelodysplasia and possibly more so in those who develop acute myeloid leukaemia.[46] The other main line of scientific investigation involves the possible role of putative repressor genes in the regions of chromosomes 5 and 7 frequently involved in myelodysplasia. The hypothesis is that loss of the normal allele could result in the unmasking of a recessive mutant allele on the remaining chromosome, as occurs in retinoblastoma. The relevant chromosomal regions certainly contain the genes for a tantalising array of growth factors and other important compounds—for example, 5q23–31 contains granulocyte/macrophage-colony stimulating factor (GM-CSF), interleukin 3, macrophage-colony stimulating factor (M-CSF), and *c-fms* (the M-CSF receptor). Similarly 7q is the site of the erythropoietin gene, the *met* proto-oncogene, and the multidrug resistance gene (MDR-1).[46]

Treatment options

Having completed the investigations detailed in table 2, one is then faced with several dilemmas. Most children with myeloproliferative/myelodysplasia have an extremely poor prognosis although occasionally there is a long prodromal phase during which the patient can be very well; Philadelphia chromosome positive chronic myeloid leukaemia is the best example of this phenomenon. It is in fact quite easy sometimes to be lulled into a false sense of security when in fact a knowledge of the extremely poor prognosis should stimulate a search for possible curative options. The management of chronic myeloid leukaemia has been very well reviewed elsewhere[5–10] and basically comes down to looking for one type of bone marrow transplantation or another. Looking after these children is a great challenge for paediatric haematologists and I will briefly review the limited therapeutic armamentarium.

Various chemotherapeutic regimens have been tried in myelodysplasia with palliative and curative intent. Other than using intensive chemotherapy for patients who effectively have acute myeloid leukaemia these have been singularly unsuccessful in achieving the latter goal.[47] However, we have now given six children with infantile monosomy 7 myelodysplasia combination chemotherapy and two remain in remission four and five years from chemotherapy.[48] The lesson to be learnt here, applicable in other myelodysplasias, is that early treatment can be successful but waiting until the development of acute myeloid leukaemia appears to reduce the likelihood of a good outcome. A reasonable palliative effect can be achieved with combinations such as cytarabine and mercaptopurine[49] with some reduction of bulk disease and requirements for blood product support. These patients usually require intensive supportive care with antimicrobial agents, blood, and platelets especially if the plan is to attempt a curative bone marrow transplantation.

There is a current vogue for cytokine treatment and many consequent publications.[50] The most commonly used at present are GM-CSF and granulocyte-colony stimulating factor. To cut a long story short, it is usually possible to improve neutropenia but not thrombocytopenia. The worry of course is that the neutrophil dysfunction will not be improved and the underlying disease will be 'cranked up'. Randomised trials are in progress so we should eventually know if these expensive compounds will help. It is also interesting to note that patients with JCML have abnormal cytokine production and regulation, which opens up the possibility of treatment with inhibitors or regulators of cytokines when these become available.

Bone marrow transplantation

As previously stated, myelodysplasia with a good prognosis (basically refractory anaemia and RARS) is a rarity and the main consideration is, having improved the child's general health as far as possible, whether a donor for bone marrow transplantation is available and if not whether a matched unrelated donor can be found on the various donor registries. The decision to go ahead with bone marrow transplantation using a matched unrelated donor can be difficult especially in a currently well child because of the relatively poor results and high mortality at present. However, techniques are improving and for almost all patients it will be their only chance of cure.

There are few published reports of the outcome of bone marrow transplantation for myelodysplasia and even fewer related to children. Matched allogeneic transplants have been associated with survival beyond three years of approximately 45%. The evidence is limited but bone marrow transplantation is undoubtedly the most effective treatment for myelodysplasia in adults and children. What is not known yet is whether one can get away with a chemotherapy 'conditioning' regimen rather than the conventional cyclophosphamide plus total body irradiation approach which is associated with major endocrine, growth, and other late effects. Preliminary studies in childhood chronic myeloid leukaemia suggest that the chemotherapy only approach may be suitable especially for very young patients.[51] Successes in bone marrow transplantation for JCML have been reported from Seattle with three of six children receiving a graft from a compatible sibling and three of eight using a donor with a 1–3 antigen mismatch alive and in remission after the use of cyclophosphamide and total body irradiation.[52] In this situation one case report suggests that a chemotherapy only regimen may not eradicate the malignant clone.[53] We have also performed a successful bone marrow transplantation in a child with monosomy 7 myelodysplasia using a histocompatible sibling and a chemotherapy/total body irradiation regimen.

The problem is that only one in three children will have a histocompatible sibling donor and now great efforts are being made to improve the chances of finding a matched unrelated donor rapidly and carrying out a successful bone marrow transplantation. Results in children with chronic myeloid leukaemia show an acturial event free survival of 30% at 30 months,[54] suggesting that this approach should be considered for all patients who do not have a sibling donor.

Conclusion

I hope that I have made it clear that the myelodysplastic syndromes are worthy of more attention both scientifically and clinically. We badly need more studies designed to determine the real prognosis and incidence of these disorders and to test the efficacy of modern treatments such as bone marrow transplantation and cytokine therapy. At a more fundamental level scientific investigations should lead to a better basic understanding of leukaemogenesis.

At long last we are beginning to understand more and to cure some of the patients but for the foreseeable future any child presenting with myelodysplasia will continue to tax our understanding and management skills to the limit.

Many thanks are due to Professor Judith Chessells, without whose help and guidance this article could not have been produced

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Archives of Disease in Childhood 1992, 67: 967–970

Children of parents in prison

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Every year in England and Wales 100 000 children lose their fathers to prison[1] and an unknown number, in excess of 3000 suffer their mother's imprisonment.[2] In many cases the parent was a single parent, and in some cases both parents are convicted and imprisoned for the same offence simultaneously. This paper examines the fate of these 'orphans of justice',[3] looks at the provision for children to accompany their mothers to prison and whether it meets the children's needs, considers the role of health care and other professionals in the care of these children, and makes recommendations for improvements in the provision of services for families caught up in the criminal justice system.

Children of criminal fathers

Findings from several studies indicate that having a father who has committed a crime is a risk factor for delinquency in boys.[4] This risk is compounded by the absence of father from home for long periods during childhood. Studies of the impact on families of the loss of father to prison help us to understand why these children are at such high risk. A study by Shaw of 415 men received into a prison with a sentence of six months or less found that about half (194) were married or cohabiting and had responsibility for more than 378 children. The same sample had a further 196 children with whom they were no longer living because of divorce, separation, or desertion.[3] Four of the men were single parents. On the basis of these findings, Shaw estimated that in 1984, the year of the study, approximately 75 000 males over 21 years of age were received into prison who would have between them about 100 000 children. There would in addition be children of younger men. Thus, more than half a million children under 16 years have experienced the imprisonment of their father on one or more occasions—that is, 5% of all children in England and Wales.

These children are among the most deprived in our society and their father's imprisonment compounds their deprivation as their mothers struggle to cope with debt, poverty, loneliness, ostracism, stigma, and homelessness. In addition, they encounter difficulties that other single parents do not. They may not know where their husband is; they may arrive at a distant prison for a visit, encumbered by children and their paraphernalia, after a long journey by inadequate transport only to find he has been moved without notification. Visiting areas are often unsuitable for children, drab and uninviting, with few toys, little space, and no privacy for intimate discussion. The women feel they have to put on a brave face and cannot tell the fathers their problems. The men often ask for supplies that can be ill afforded but cannot be denied them without their women revealing their destitution. One study found that on average each man in prison is supported by his family to the tune of over £500 per annum,[5] which has to come from the meagre provision made by the state for prisoners' families, thus impoverishing them further.

For many of the mothers, a father's imprisonment means the loss of their only source of income and financial knowledge and skill. The mothers are fearful of asking for state help in case their children are removed from them and they are often ignorant of their right to benefits.[6] There is no statutory provision for them to receive such information, and the probation service is seen as giving help to offenders rather than their families.[7] They tend to borrow from family, friends, and from loan companies with high rates of interest, impoverishing the family further.

Often other agencies, schools, health visitors, and social services are unaware of the incarceration of the father,[7 8] and two thirds of mothers conceal the fact even from the children and their own families, using such evasions as 'working away' or 'in hospital'. The children therefore often learn of their father's imprisonment from other children or, not knowing, feel abandoned by him and fear that their mother may do the same.[1]

It is difficult for children to have access to their fathers frequently enough to maintain a relationship, and this leads to problems on release. There are other problems related to the fact that prison in many ways infantilises the men, while the women outside have matured through having to manage children and finances alone. Many of the women fear their man's release because they do not wish to revert to the previous dependent state. The lack of adequate prerelease home visits and difficulties in communication mean that adequate preparation has not been made to deal with these difficulties.[5]

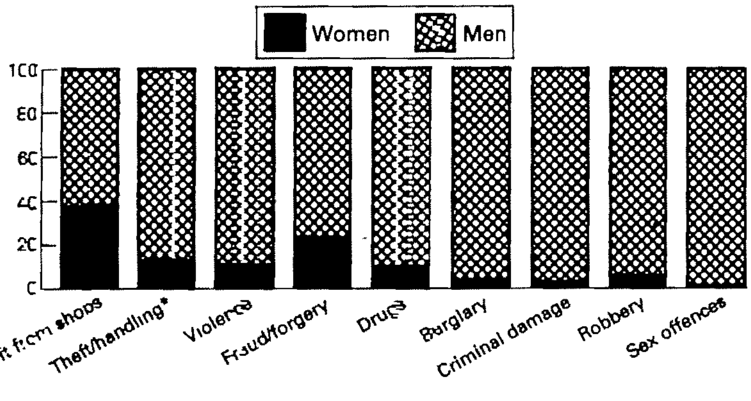
For some children and families the imprisonment of father may be a relief if it removes an abusive, violent, or spendthrift man. These children and their mothers may resist attempts by father to have them visit him, and it is unclear whether the new provisions of the Children Act 1989 concerning continuing parental responsibility will affect the children's right to refuse to visit. Children whose father kills their mother may have witnessed the killing, and of those who do a high proportion develop a psychiatric disorder, notably post-traumatic stress disorder and conduct disorder.[9] Many of these children fear their father and hate him for depriving them of their mother. As they are effectively parentless they suffer more trauma as attempts are made to find them a home, and the families of the mother and father battle over their custody or give inadequate care because of their own grief and anger. These children more than those whose mother is caring for them suffer from changes of carer, home, school, and friends. Their burdens may be increased if they live with paternal relatives who see it as their duty to maintain the children's contact with the feared and hated father.

The children of a man who was already separated from their mother before his arrest may have limited or no access to him after imprisonment, even though they enjoyed contact with him before, as there may be no one willing to take on the job of accompanying them to prison. It is the right of the child to be accorded contact with the father but, in practice, this right like many others may be denied them.

The children too find themselves stigmatised at school by their father's crime. Surprisingly little research is available on the psychiatric disorders or school problems of prisoner's children. Richards has suggested that the effects on children of their parents' imprisonment is similar to those of divorce but that, in addition, imprisonment may lead to divorce so that a child may suffer from both kinds of upheavals.[10] He draws attention to the high incidence of behavioural and other psychiatric problems in children of divorce and concludes that children of prisoners will be at high risk of similar problems.

Children of imprisoned fathers therefore suffer all the disadvantages of children of single parents (poverty, homelessness, maternal depression) with the added difficulties of shame, stigma, inadequate information, and loss of contact with the father. They may have to cope with their anger and fear of a father jailed for killing their mother or sibling, or who physically or sexually abused them, who nevertheless has the power to compel their attendance at a prison which may require, in addition, that they undertake a harrowing journey.

Their role model for male behaviour on the other hand may be that of a glamorous hero whose exploits bring pride and status to the family. This may be particularly so in the case of terrorist activity.[11] In either case the evidence is that having a criminal father enhances the likelihood of male delinquency and female social difficulties.[4 10]



Percentages by sex of persons found guilty or cautioned for indictable offences in 1989.[16]
**Excludes theft from shops.*

Children of criminal mothers

Most children whose fathers go to prison remain with their mothers. When mothers are imprisoned, fathers rarely care for them and they face much more disruption in their care, place of residence, and school.[12 13] The problem is much smaller numerically, although exact numbers are difficult to ascertain as some women who are imprisoned refuse to reveal the fact that they have dependent children, fearing that the children will be taken into care and will not be restored to them on their release from prison. Woodrow has calculated that at least 3000 children a year are affected by their mother entering prison.[2] In addition, about 70 babies a year are born to women serving prison sentences—usually accommodated in NHS hospitals with an accompanying prison officer for the birth. One third of the women had children under 4 years of age.

A small proportion of imprisoned women will be allowed to have their infants with them in prison. There are three women's prisons in England and Wales (none in Scotland or Northern Ireland) which accept a total of 36 babies in all: at Holloway (London) and Styal (Cheshire) they can stay until 9 months of age, and in Askham Grange (an open prison in Yorkshire) until 18 months.

Far fewer women than men offend and their offences are overwhelmingly non-violent. About half a million offenders were found guilty or cautioned for indictable offences in 1989. Of these, approximately 83% were men and 16% women.[14] The figure shows that compared with men, women's offences are overwhelmingly non-violent. Half of the prison sentences for women were for non-payment of fines; the majority of mothers in prison are remand prisoners, of whom only one third will eventually receive custodial sentences.[15] Unfortunately there is a trend to use prison increasingly for first offenders, both men and women.[16]

The children remaining outside are cared for in the main by relatives, usually middle aged or elderly and often as financially and socially disadvantaged as the mothers themselves. Some children go into local authority care, and many of those have more than one foster parent during the sentence (L Catan, B Lloyd, unpublished report, 1989). The children may also be separated from siblings and their father,[17] or older siblings may have to do much of the parenting. When the mothers leave prison they are often in great debt, with rent arrears or no accommodation and unable to find employment. They cannot therefore take back their children and may find themselves forced back into relationships with violent and alcoholic men.[13 18]

In 1986 a census was taken of 11 prison service establishments for women in England es. This showed that 340 women rs had 455 children under 5 years of age, of the children were in mother and baby units with their mother, 69% were with relatives, 7% were with friends, 19% were in care, and 1% had details unknown.[19]

Those few children who accompany their mothers into prison have problems brought about by their own incarceration. Catan was commissioned by the Home Office to study the development of babies in prison.[20] Using monthly recordings of the Griffiths's scales she found that, compared with those of similar age left behind, there was little difference in overall development (most babies were in prison for a short time—weeks rather than months). The test scores of babies who spent longer than average in the units revealed a gradual developmental decline over a four month period in two areas of development only—locomotor and cognitive. The developmental levels of babies left outside did not change over a four month period from the start of their mothers' sentence, unit babies' scores declined gradually and, by the fourth month, there was a statistically significant difference between the score of the two groups which increased with time spent in the prisons. In a later study, Catan and Lloyd established that the most likely cause of this discrepancy was the lack of stimulating toys and everyday objects, and the reluctance of the mothers to allow the babies to sit and crawl on the floor because of hygiene and interference from other mothers and children (L Catan, B Lloyd, unpublished report, 1989). The children spent long hours strapped in prams, chairs, and bouncers or being carried around.

One of the factors mentioned by the authors of the study was the lack of child centred expertise available to the mothers. Health visitors' visits were sporadic or lacking and the professional expertise of nursing and prison staff lay in directions other than child care and development. As a result of these studies efforts are being made to remedy some of the deficiencies identified. One major advantage of the children being with their mothers is the close bond that they develop. It is therefore distressing to learn that the admission criteria for babies and children, as set out in Circular Instruction 51/1983, are determined by the Home Secretary guided by the prison governors—who depend on considerations other than the primary one of the child's welfare. The availability of places, the length of the mother's sentence, her freedom from mental and physical illness, and her parenting ability have all to be evaluated by them and although they should seek advice from health, probation, and social services they are not compelled to do so.

Parenting ability is very difficult to assess and requires a high level of skill and experience.[21 22] Similarly the assessment of mental and physical illness and its effect on parenting ability is not a simple matter and requires medical, psychiatric, and psychological knowledge unlikely to be within the compass of a prison governor or even some of his regular advisors.

An assessment of eligibility is made by the governor of the holding prison and conveyed to the governor of the appropriate prison, so the mother is imprisoned initially without her baby while the assessment is made. An overriding criterion is the likely length of the mother's sentence. If the baby will reach 9 or 18 months before the mother finishes her sentence, the baby cannot be admitted. In practice this apparently sensible ruling is not adhered to: babies who may have had an unusually close and intimate relationship with their mother for nine months can be abruptly taken out of the prison to other carers. A governor can and has caused a baby to be removed from prison as a disciplinary measure—with no requirement to consider the needs of the child as paramount. A challenge to that decision was not upheld by the High Court (R v Secretary of State for the Home Department ex parte Hickling and J H (a minor), 1986).

Imprisoned children have virtually no contact with other members of their family and their separation if it is necessary after nine months can rarely be managed slowly. Separated children cannot be brought to prison frequently enough to mitigate their pangs of grief at the separation.[23]

Needs of children

Apart from physical nurture, and protection from harm, young children need the contiguity and continuity usually supplied by their parents, in order to develop emotional security as a prerequisite to intellectual and physical development. Because they have so little experience, many events or situations evoke fear and anxiety in a small child and these experiences are modified in the presence of their attachment figures.[24–26] Disruption of attachment bonds seems to be particularly dangerous between the ages of 6 months and 4 years but it may be damaging earlier. There is evidence that young children who have sudden or repeated separations are more likely to develop psychiatric disorders and are more prone to deviations in personality development, leading to aggressiveness, coldness in personal relationships, difficulties in learning, and a greater tendency to parenting difficulties in adult life.[27] Children whose attachments are disrupted also have many other disadvantages that are probably cumulative and interactive but it behoves a caring society to try to minimise the number of adversities to which children are subjected.

ARE THESE NEEDS BEING MET?

Children caught up in the criminal justice system because of their parents' offences are innocent victims. Shaw points out that the question that should be asked is not what harm is done to these children by the imprisonment of their parent, but why this harm is permitted and, in some cases, made to happen.[28] Prisoners' families suffer from being seen as 'undeserving' or stigmatised as having brought it on themselves.[29] Shaw asks whether it is just to punish the innocent more than the guilty, or indeed the victims of the offenders. 'The majority of persons received into British prisons under sentence in default of payment and on remand remain there for less than three months and many for only a few days or weeks . . . One is forced to ask whether the incarceration of these short sentence prisoners be justified if the children of a significant proportion suffer harm as a result? As we have seen, most women prisoners fall into this category.

Inspired by a television programme which reported a similar initiative in New York, Holloway prison introduced improvements to the facilities for children visiting their mothers.[30] Two Sundays a month the children that are separated from their mothers can stay with their mothers for the day in the gym and education block. This is not available for remand prisoners, and while the initiative should be welcomed, it is only likely to be of benefit to older children. For children under 5 years the long gap between visits makes it unlikely that the pangs of grief will be assuaged, and indeed they may be tantalised by the renewed intimacy, only to be sundered again.

RECOMMENDATIONS

Children need their parents to care for them. Most criminal parents can parent well. Children deprived of their parents rarely find better substitute ones and our society is not meeting the needs of children of offenders. If we are to admit young children to prison with their mothers, we should be providing facilities of the same standard as is mandatory in social service day nurseries. If the children have to be taken from their mothers in prison, the management of the separation must be done gradually, in order to enable the child to attach to a new caretaker before relinquishing the first one. Children's welfare in the prison must be the responsibility of someone of high enough status and sufficient knowledge of children's needs to be able to influence policy and practice. I suggest that this should be a consultant community paediatrician and that the child's welfare, in prison as elsewhere, should be regarded as paramount. All children in prison should have the services of nursery nurses, and a health visitor, and provision should be made for a budget for toys, furnishing, and equipment.

Similarly, community paediatricians working in schools should be aware of prisoners' children and, with the school, monitor their mental health and welfare and that of their family.[8 31] Health visitors should be made aware through the probation service of those preschool children whose parents are imprisoned.[7] Parents in prison should be granted home leave early and should be enabled to keep in touch through provision of telephones and better facilities for children to visit.[31]

No mother or single father should be given a custodial sentence without the judge or magistrate satisfying himself or herself that proper provision has been made for the children. But need so many parents be imprisoned? If a non-custodial alternative is appropriate should we not use it? Other countries have found it possible to use
community servic
no higher than ours.

Legislation may be
children and parents are n
Unless the public needs to be pro
murderers, some violent offenders, so
offenders, and some mentally ill offenders), doctors should use their influence as citizens through their parliamentary representative to prevent unnecessary imprisonment of parents.

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Archives of Disease in Childhood 1992; 67: 971–975

TYPES OF PSYCHIATRIC TREATMENT

Psychiatric treatment for children—the organisation of services

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The Court report in 1976 laid down the classic blueprint for the organisation of children's mental health services.[1] Since then the priorities of health and other services have changed.[2] Social services in some parts of the country have had to redirect social workers from child guidance to child protection work, often because of the major increase in reporting of child sexual abuse, and now also have to consider the implications of the Children Act.[3] Education services have had two major education acts to deal with,[4 5] and they are subject to the turbulence of further continued reform.

This paper looks at dynamics more than structures and offers observations on how modern approaches, especially of health economics, are shaping an inner London child psychiatry service in the new context of the NHS reforms.[6]

(A) Methodologies to improve services

1. MARGINAL COST-BENEFIT ANALYSIS

Marginal analysis in health economics is a method of evaluation when planning a service programme to find the most cost-beneficial way of proceeding.[7] The approach of marginal analysis:

(a) Acknowledges the limitations of resources. The child psychiatry service probably has a fixed budget, and opportunities for increased funding look limited.

(b) Proceeds from current available resource provision and use. The first step in planning is not therefore to survey the hypothetical 'child psychiatric needs' of the whole population and from this recommend 'ideal provision', but to look at current provision, its uptake, and effectiveness.

(c) Tries to establish priorities for a given type of provision, rather than to set an arbitrary standard. It seems difficult in the usual multidisciplinary child psychiatry setting for instance, to answer the question 'Which cases would not benefit from long term child psychotherapy?'. On the other hand, a 'marginal' type of question—'What sort of cases have in the last year benefited least from long term individual psychotherapy?' has been found to be more readily answerable, and provides an opportunity for the future more effective direction of resources.

(d) Tries to identify the range of costs, both for the service and its users. These could include for the child and his or her family attending child psychiatry outpatient appointments for example distress, stigmatisation, loss of education and income, and disruption of household arrangements. For the child psychiatry service costs could include not only the resources devoted to the treatment, but also the stressfulness of the case, and the opportunity cost of not offering the resource to another, more responsive, case.

(e) Tries to identify the range of benefits, for instance, acceptability, availability, efficacy of treatment, accessibility, and equitability. In child psychiatry the child whose symptoms are relieved is not the only beneficiary; there are gains for the parents and siblings, and often also the school. 'Benefits' for the service could include contributing to the fulfilment of the service contract, the opportunity for learning and research, and variety.

(f) Concentrates on marginal rather than average costs and benefits. So far, costings in child psychiatry are very rudimentary, due to the non-standard nature of problems, situations, and interventions. However, it is clear that it would be cheaper (and easier) for an established programme—say of group work for sexually abused children—to take on a few extra cases, than it would be to provide a new, similar programme for a small number of children not far away. This is even more obvious for expensive provision such as adolescent inpatient admissions.

(g) Establishes a framework in which judgments of relative benefit are made explicit and thus trade offs are clearer. Although formal quantification of costs and benefits is limited and difficult in child psychiatry, informally extreme categorisations of the cost:benefit ratios of cases have been found acceptable and are the subject of further study. For instance, most clinicians, when asked, could respond to the question 'Which of your recent cases represented the poorest clinical gain in relation to the resources put in?' Then, if such cases have common characteristics, there is the possibility of considering limiting input at an earlier stage, in order to devote resources elsewhere.

2. AUDIT

For child psychiatry, audit offers a way of improving treatments and services using local data and nationally available information educationally, even when the resources and opportunities for mounting double blind controlled trials are not available.

In our district, multidisciplinary audit in child psychiatry is being used explicitly to improve the service offered at a number of levels as recommended by the Royal College of Psychiatrists.[8]

(a) Team level

i. Quality of case notes—extremely simple standards have been found to be robust but revealing:

- Can the file be found?
- Is the cover/front sheet information complete?
- Are the notes filed correctly?
- Is there a typed first assessment?
- Have the general practitioner (GP) and referrer been informed of the outcome of assessment?
- Is there a note of action in the last six months, or a letter to GP and referrer advising of closure?

After 15 months, standards have considerably improved.

ii. Commissioners' requirements—This year the commissioners asked for the following to be audited:

- Following a GP referal, in 80% of cases a meaningful reply should be sent to the patients/clients within two weeks,
- Time for response to GP after first assessment to be reported,
- Waiting time for appointment.

Auditing these has also led to an improvement in standards, although more administrative support and appropriate computerised information systems are necessary for full implementation.

(b) Interteam level

The four consultant teams of the district hold audit meetings each term with an educational focus on topics of major treatment relevance, to consider current practice and 'best practice' advice, and how to modify management in the light of this. 'Soiling' and 'hyperactivity/conduct disorder' have been considered so far.

(c) Planning group level

At the district planning group level service relevant audit is coordinated by means of:

- General information review,
- Promotion of specific audit projects,
- Organisation of other quality oriented projects such as patient satisfaction surveys, etc,
- Resource issues review,
- Coordination of other audit results for annual review and report to commissioners,
- Liaison with other audit committees within the hospital and at regional level.

3. OUTCOME MEASURES

Outcome studies of treatment in child psychiatry are being more frequently performed now, and are encouraging,[9–11] but outcome measures suitable for general use are not yet available. This is not surprising given the variety of contributory factors to childhood mental disorder, the degree of comorbidity, and the eclecticism of interventions. As databases become more widespread, however, it is worthwhile beginning with what seems feasible locally.

(a) Administrative outcomes

Administrative outcomes are the simplest to determine, and are worth monitoring—for example:

- Referral not accepted,
- Referral withdrawn,
- Case attended,
- Case never attended.

Referrals have been monitored on this basis at local clinics for a number of years, so comparisons and trends are apparent. Other clinics have found useful slightly more complicated categorisations, adding in mode of discharge.[12 13]

(b) Therapeutic outcome measures

Systematic attempts to measure therapeutic outcome are now being evaluated.[9] What should be done with outcome measure results? At present, differences between different centres for apparently the same condition would be very difficult to evaluate, but within the same centre outcomes should be an aid to decision making. Repeated measures of progress on individual cases would also be a guide to when intervention could be terminated.

In the future, quality adjusted life year (QALY) type measures may be evaluated,[14] to answer not only 'within-programme' but 'between-programme' questions, such as—what are the comparative costs and therapeutic gains of an average child psychiatry and an average paediatric course of treatment?

(c) Performance indicators

The national requirements of the Korner report are ill suited to child psychiatry,[15] but are still collected through most hospitals' patient administration systems. A survey conducted by the author of all consultant child psychiatrists in the region revealed that each Körner information requirement was interpreted variously. As a result of attempts to increase local validity (meaningfulness), central reliability was completely lost. However, as Jenkins has rightly pointed out, process measures should not be used as a proxy for outcome measures.[16]

(d) Health outcomes

The monitoring of childhood 'health states' such as the parasuicide and suicide rates, the incidence of psychiatric disturbance, and the emotional impact of psychosocial disadvantage, has been recommended as an appropriate method of measuring outcome for child psychiatry.[16] This appears bizarre to the clinician—rather like judging the performance of the accident and emergency consultant by the number of road accidents, and shows how important it is to have agreed objectives for a service before setting out to measure its effectiveness. However, population morbidity measures (such as the child abuse rate) could certainly help to indicate priorities for intervention.

4. CONSUMER RESEARCH AND QUALITY

'Consumerist' approaches are now important in evaluating, and therefore determining, services. Who is the consumer in child psychiatry?

(a) The child and the family

i. Preparatory information—A local survey[17] supported other findings[18 19] that parental understanding of child psychiatry services is limited. As outcomes may be better if expectations of family and clinic are congruent,[20] we have reviewed information sent out at the different clinics and are in the process of improving it.

ii. Improving attendance rate—Non-attendance at appointments is commonly noted in child psychiatry,[13] and can be a considerable waste of professional time. Following the suggestion to telephone some families beforehand has helped reduce the non-attendance rate in one of the local teams.[21 22] Requiring questionnaire completion was thought to be too demanding for our population,[22 23] as even routine confirmation of appointment is only erratically complied with.

iii. Waiting time—A local survey showed that parents who thought the wait for appointment was 'too long' had waited an average of 8·6 weeks; parents who thought the wait was 'OK' had waited a mean of 7·1 weeks.[17] Efforts are made to keep the waiting time down to six weeks if possible. If, as has sometimes happened due to staff cuts, a waiting list of three months develops at a clinic referrers are advised about alternatives.

Although a longer waiting time for an appointment has been noted to reduce likelihood of attendance,[24] audit of one local team's attendance rate showed a surprising tendency for offer of a rapid appointment (within 1–3 weeks) to be associated with a higher failure rate, so that time taken over checking willingness to attend was concluded to be more important.

iv. Patient satisfaction: process—Satisfaction with such 'process' variables—such as ease of finding the department, the pleasantness of the waiting area, the acceptability of the toys and reading material—is currently being surveyed in our hospital department. It is hoped that this will reveal opportunities for improvement, and also possibly provide ways of comparing different sites in a standardised way, and where necessary underpin arguments for upgrading of facilities.

v. Patient satisfaction: outcome—Successful attempts to measure parents' views of outcome have been reported.[9 25] As satisfaction is likely to be increased if treatment goals with parents and or children are agreed a goal attainment rating scale is being tried locally as a first step in this direction, and we are considering making it more 'computer game-like' to interest the children.

vi. Acceptability—The local child population is very mixed culturally, with the largest minority ethnic group being Afro-Caribbean. We have aimed, in the last few years, to make the service more acceptable to ethnic minority families, and have undertaken appropriate staff education, appointed more ethnic minority staff members, and offered training specifically to ethnic minority students. Finding appropriate toys is not easy, but is visibly appreciated. There is no longer a marked difference in uptake between the hospital and community provision.

(b) Other health professionals

GPs, hospital and community paediatricians, health visitors, and school nurses can also be customers of child and family pyschiatry services. Dissatisfaction can easily arise if there are situations of high risk and/or distress, and the child psychiatry service seems slow or remote. This can occur not merely through the limitation of resources, but because 'child guidance' had until recently little relationship with the primary health care system. Improving communication must therefore be a priority, as GPs themselves are making clear.[26]

i. Information—Referrers' knowledge and expectations of the services of one of the local child guidance units were found to be more accurate then the parents', but still somewhat vague.[17] Leaflets describing clinic services were in popular demand previously, and need updating. There is an active department of general practice, through which other information is disseminated, and occasional 'Meet the GP' sessions are arranged.

ii. Letters—Even though many referrals to children's mental health services are not from GPs, there is usually a policy that the GP should be kept informed. Audit of our own practice in this respect showed a frequent deficiency but is now improving.

iii. Liaison—Over the last few years we have increased outreach to GPs[27] and liaison with hospital and community paediatric services including health visitors. The impact of these efforts is difficult to quantify, but they are all subject to review and are dropped if not successful or if other provision becomes available, such as the appointment of a specialist counsellor. Requests for further involvement or for training are encouraging.

iv. Satisfaction—Locally, surveys of GP satisfaction have so far been carried out at hospital and general psychiatric service level only, but elsewhere surveys of the satisfaction of GPs and health visitors with their local child and family psychiatric service with informative results have been reported.[28,29] Such surveys are now being requested by commissioning authorities, and they offer an opportunity to identify deficiencies that may support requests for more resources.

(*c*) *Education and social services*

Locally, as with many 'child guidance' services, referral has been open to education and social services; clinics were planned, staffed, and administered with the local authorities. Satisfactory relationships with the local authority agencies are therefore crucial to the maintenance of the service, but may not be enough with local government budget pressures and competing statutory priorities.[2]

i. Social services—Our service offers regular liaison to area offices, arranges meetings at senior level to discuss priorities, offers training courses, and attends committees such as the Area Child Protection Committees and Joint Care Planning Groups. Nevertheless hospital social work has been subject to freezes and cuts, and unrealistic expectations easily arise with respect to the child psychiatry service's appropriate role in and capacity for child abuse work. (Involvement in child abuse can be a major part of a child mental health service's work, but is exceptionally consuming of resources.[30,31]) 'Public relations' work is therefore constantly necessary.

ii. Education—Since the abolition of the Inner London Education Authority the funding for the non-health professionals in the two local child guidance units has been under repeated threat. However, while resources are being put in by education, it is important to work out priorities with them—an example is working to prevent expulsion from school, rather than spending a lot of time on special educational assessments after the event.[32]

(B) The purchasing environment

1. COMPETITION OR COLLABORATION?

Improving efficiency is a clear aim of the NHS reforms, but the emphasis is more on costing throughput than clinical outcome, and the intended method is that of the market, which can produce distortions.[33,34]

Although many small child psychiatry services are potentially monopoly providers, in a large city such as London purchasers might theoretically invite competitive tenders. As there is no obvious 'spare' capacity currently this would be wasteful of resources as cost differences between services are likely to be partly due to inaccurate allocation of costs, and differences of 'case-mix'. Encouraging collaboration between adjoining services would be a better strategy for ensuring the availability of a comprehensive but mainly community based services, with some possibility of consumer choice. Standardisation of information collection and quality ratings would be helpful and some specialisation at different centres might lead to greater efficiency at the margins.

2. DEMAND AND NEED

Basic epidemiological information is already available in child psychiatry, including knowledge of the social concomitants of childhood disturbance that are more readily measurable.[35–37] 'Need' in child psychiatry is usually estimated to be much in excess of potential sources of help, but 'needs' are relative and are meaningless without a notion of possibilities of amelioration.[7,38] 'Demand' can be very much altered by for instance publicising a service, and waiting lists can expand or contract according to the way they are managed. Purchasers should therefore be aware of the relativity of both demand and need.

3. OBJECTIVES, VALUES, AND PRIORITIES

The purchasers' responsibility is to procure the best possible value for money health services for their population. Accepting that resources are always limited, in child psychiatry some 'quality values' may have to be traded off against each other: accessibility versus initial consultant assessment, for instance, or comprehensiveness of case notes against information returns. Choices will have to be made over the use of time—for example, should a court request for assessment take priority over GP referred cases? Should there be more psychological support for terminally ill children and their families, or should there be a specialist team for autistic children? There must be discussion between purchasers and providers about objectives and values, which can lead to the establishment of agreed principles to determine priorities. Priorities should be considered in conjunction with those of the local paediatric and psychiatric services and of GPs. The local authority should also be consulted, to maintain and develop collaborative service arrangements.

In conclusion, the reorganisation of the NHS has produced many challenges but within it there are also opportunities for rethinking how to make the best use of child psychiatry services to reduce the burden of mental health problems for children now, and for their future adult lives.

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Brittle bones and battered babies

The late Dr Leonard Taitz of Sheffield provided much in the way of clear thinking about the problems of child abuse. In a leading article in the *British Medical Journal* in 1987 he discussed the diagnosis of osteogenesis imperfecta in children with unexplained fractures.[1] Of the four types, type 1 (80% of all osteogenesis imperfecta) is almost always associated with blue sclerae. People with types II and III have multiple fractures and skeletal deformity. These three types should not pose a problem in the differential diagnosis of child abuse. Type IV osteogenesis imperfecta is less severe and the sclerae may be normal. Fractures in this type of the disease could possibly be mistaken for inflicted injury. About 5% of all cases of osteogenesis are type IV. Many will have a family history of osteogenesis or dentinogenesis imperfecta. Dr Taitz calculated the incidence of type IV disease with no family history and normal sclerae to be between one in a million and one in three million. He postulated that the absence of multiple wormian bones on skull *x* ray film after the newborn period virtually excludes the diagnosis.

It is now possible to diagnose osteogenesis imperfecta by analysis of type 1 procollagen in skin fibroblast cultures and workers in Tucson, Arizona (Sheila Gahagan and Mary Ellen Rimsza, *Pediatrics* 1991;**88**:987–92) have described three children who were thought at first to have suffered non-accidential injury but who were shown in this way to have osteogenesis imperfecta type IV. One of these children, however, had blue sclerae, one was thought unlikely to have accidental injuries on clinical and social grounds, and one had a sibling with osteogenesis imperfecta and had suffered fractures while in the care of several different people. There were, therefore, good clinical reasons for rejecting a diagnosis of non-accidental injury in all three cases and they do not detract from Dr Taitz's contention that it is possible to exclude the suggestion of brittle bone disease in almost all cases with a good history and clinical and radiological examination. Where there is genuine doubt collagen analysis may in future provide an answer but it should rarely be necessary.

ARCHIVIST

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REGULAR REVIEW

Recent progress in intestinal transplantation

Celia Ingham Clark

Transplantation of the kidney, liver, or heart is now a well established and successful treatment for irreversible organ failure. It has been much more difficult to achieve success in intestinal transplantation, although experimental and clinical work has been carried out in this field since the late 1950s. However, in the last three years there have been several successful human small bowel transplants in both adults and children. The problems associated with intestinal transplantation include difficulties with preservation and operative technique, as well as a high incidence of rejection, graft-versus-host disease (GVHD), and postoperative infection. These problem areas are discussed and the history of human small bowel transplantation is reviewed.

Indications for transplantation

Intestinal failure can be defined as an inability to maintain nutrition and/or positive intestinal fluid and electrolyte balance without special measures.[1] This may follow massive resection or may be caused by motility disorders or extensive disease inhibiting absorption. The commoner causes of irreversible intestinal failure include congenital atresias, gastroschisis, volvulus, and necrotising enterocolitis in neonates,[2] volvulus, visceral myopathy, and mucosal abnormalities such as congenital enteropathies in older children, and Crohn's disease, resection for volvulus or desmoid tumours, and mesenteric infarction in adults.[3]

In most cases of intestinal failure, especially those in infants, the residual intestine adapts, although it may take over two years to achieve resumption of a full enteral diet.[3] Factors that mitigate against reversibility of intestinal failure are excessive loss of healthy bowel in relation to total length for age,[2] absence of the ileocaecal valve and right colon,[4] and poor function of the residual intestine.[5] In some patients adaptation is insufficient to permit cessation of parenteral nutrition and intestinal failure is therefore permanent. At present, individuals in this group who survive are committed to permanent parenteral nutrition. Even if this can be delivered at home, it is associated with a very abnormal lifestyle and with complications which include sepsis, central venous thrombosis, and metabolic disorders.[6] For patients with irreversible intestinal failure, transplantation should be the treatment of choice. However, the results of transplantation to date have been so poor that parenteral nutrition has been the safer option. This situation may be changing.

Problems are associated with small bowel transplantation because the intestine is one of the largest lymphoid organs in the body. In addition there are normally bacteria within the gut lumen, and the mucosa is extremely sensitive to ischaemia. The large lymphoid content of the small bowel renders it highly immunogenic. It is also much more liable to initiate GVHD than other solid organ grafts. The bacterial content has the potential to cause systemic sepsis if the mucosal barrier is damaged. The sensitivity to ischaemia makes it difficult to successfully preserve the small bowel in vitro.

Donors

Although there are theoretical immunological advantages in using live related donors, it may be difficult to harvest a long enough segment of intestine to permit adequate graft function in the recipient without compromising the nutritional status of the donor. Transplantation from mother to baby may avoid this problem as a relatively short graft would be required. Most human transplants have been performed using cadaveric donors. This is associated with a greater discrepancy between histocompatibility antigens in graft and host and therefore a greater risk of graft rejection. In addition, most donors have been critically ill in intensive care units. During this time the intestine is often subjected to periods of hypoperfusion, and it may also contain abnormal bacteria such as *Staphylococcus epidermidis*, which can translocate from the bowel and cause systemic infection.[7]

Preservation

The ideal method of intestinal graft preservation has not yet been determined. Experimental evidence suggests that vascular perfusion with Collins' solution allows reasonable preservation for up to six hours.[8] The gut lumen also requires perfusion and cleansing, perhaps with an antibacterial agent. The mucosal sensitivity to ischaemia is important. Mucosal sloughing commences after only 30 minutes of warm ischaemia.[9] Experimental data suggest that the addition of mucosal nutrients such as glutamine may improve small bowel preservation.[10]

Technique

Standard microsurgical techniques, based on the original work of Carrell in the 1900s have been used to construct successful vascular anastomoses in small bowel transplantation.[11]

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In most instances the superior mesenteric vein draining the graft has been anastomosed to the iliac vein or inferior vena cava of the recipient. However, this effectively creates a portocaval shunt which may lead to long term complications. Graft venous drainage into the recipient portal vein, although technically difficult, is more physiological and may be associated with fewer metabolic complications.[12] Portal drainage may also convey an immunological advantage.

In most experimental and clinical cases of small bowel transplantation the graft has initially been placed out of continuity with the native intestine. This is to avoid anastomotic breakdown which would be a risk in the presence of ischaemia associated with early rejection. Therefore the ends of the graft are either both exteriorised as stomas,[13 14] or the proximal end is anastomosed to the native jejunum and the distal end brought out as a stoma.[15 16] This latter technique allows normal upper gastrointestinal secretions and enteral nutrition to flow through the graft, which should improve mucosal nutrition.[17] In either case, the graft is put into continuity with the native intestine at a second operation at a later date.

Rejection

Small bowel allografts are highly immunogenic because they contain large amounts of lymphoid material in the mesenteric lymph nodes, Peyer's patches, and lamina propria of the intestinal wall. In experimental studies in rodents, rejection has been consistently prevented with cyclosporin monotherapy.[18 19] However, results have been less consistent in large animal models.[20 21] In human transplantation rejection episodes have occurred in almost every case despite treatment with multiple immunosuppressive drugs.[13–16] The most successful small bowel transplants have been carried out using a combination of cyclosporin, azathioprine, and prednisolone with a short course of the anti-T cell monoclonal antibody OKT3,[22] or the new immunosuppressive drug FK506 with prednisolone.[23]

The diagnosis of rejection has usually been made using histological and immunohistochemical evaluation of multiple mucosal biopsy specimens.[24] However, histological signs of rejection may be patchy and multiple biopsies are necessary.[15] Because the small bowel normally contains many lymphocytes a cellular infiltrate *per se* is not indicative of rejection. Morphological evidence of rejection includes villous shortening, crypt lengthening, and epithelial sloughing, although these are late signs.[25] Early signs of rejection include loss of intracytoplasmic brush border enzymes, identified by immunohistochemical analysis[26] and a submucosal mononuclear cell infiltrate.[27] Functional tests for rejection are largely based on assessment of mucosal permeability. Absorption of ^{51}Cr-EDTA is increased in rejection, and this test has been used successfully in human transplantation.[28]

Acute rejection can be reversed in rodent models, and this has also been achieved after human transplantation. Conventional treatment such as antilymphocyte globulin or steroid boluses have achieved reversal of acute rejection.[14 16] If rejection cannot be reversed the graft must be removed promptly because in the absence of an effective mucosal barrier, bacteria can readily enter the host circulation and cause septicaemia. Once a rejecting small bowel graft has been removed the patient may revert to total parenteral nutrition, and in at least two instances a second transplant has been undertaken at a later date.

Small bowel allografts have been shown to be infiltrated by host cells in the absence of rejection[23 29] therefore immunohistochemical staining for host cells is not an indicator of rejection. Graft cells normally migrate to host lymphoid tissues after small bowel transplantation and the disappearance of graft cells from peripheral lymph nodes and spleen of the recipient is associated with graft rejection, preceding histological changes in the graft (P Lear, C Ingham Clark, *et al*, unpublished observation). Fine needle aspiration cytology of lymph nodes and staining for graft derived cells might be used as a test for rejection.

Liver/small bowel transplantation

It has been known for many years that combining liver transplantation with grafting of another organ reduces the risk of rejection of the second organ.[30] This protective effect appears to be considerable in small bowel transplantation. Combined liver/small bowel transplantation was initially performed in patients with liver failure resulting from long term parenteral nutrition,[28] but after several successful cases this technique has now been used in some patients with normal liver function.[22] This latter treatment is controversial on ethical grounds, and efforts are continuing to find better immunosuppressive treatment regimens to achieve improved results for pure small bowel transplantation.

GVHD

GVHD is a common problem in bone marrow transplantation, but rare in most solid organ grafts because they contain relatively little lymphoid tissue. It is a potential problem in small bowel transplantation because the large amount of lymphoid tissue in the graft can mount an immunological reaction against foreign major histocompatibility complex antigens of the host. GVHD will only occur if there are immunocompetent T lymphocytes within the graft.[18] Therefore treatment strategies to prevent GVHD must be directed towards these cells. In experimental models GVHD has not been completely prevented by cyclosporin treatment.[31] Pretreatment of the donor with irradiation,[32 33] antilymphocyte serum,[34] or anti-T cell monoclonal antibodies[35] can prevent GVHD. Such measures are generally inappropriate in live-related transplants. Donor irradiation may not be practicable in clinical transplantation, and the window of opportunity to treat cadaveric donors with drugs is very short.

Graft irradiation effectively prevents GVHD but carries the risk of radiation damage to the bowel itself.[36] Ex vivo graft treatment with monoclonal antibodies or anti-T cell immunotoxins has been attempted but uniform success has not been achieved.[37 38] In clinical transplantation, GVHD has developed in several patients; in some cases it has been fatal and in others it has regressed in association with changes in the immunosuppressive treatment.[14 21] Further work is required to determine how to prevent GVHD consistently.

Infection

The small bowel is the only solid organ transplant which normally contains bacteria. Flushing the lumen of the intestinal graft before transplantation will not remove bacteria that inhabit the mucous layer adherent to the mucosa, and attempts to maintain gut sterility with enteral or parenteral antibiotics and sterile food are not consistently successful. It is therefore inevitable that most small bowel grafts will be colonised by bacteria.

An important function of the small bowel is to act as a barrier against microbial entry to the body. The ischaemia associated with transplantation leads to a temporary loss of this barrier, therefore antibiotic prophylaxis must be given to cover the peritransplantation and early post-transplantation period. In rejection mucosal barrier function is impaired; bacteria enter the circulation and can be found in many organs.[39] GVHD is also associated with damage to the mucosal barrier of the native bowel and systemic sepsis.[40] Recent work has shown that the range of bacteria within the intestine changes in both rejection and GVHD. The organisms that translocate from the bowel lumen to infect the host are not all normal enteric commensals. *S epidermidis,* a common cause of multisystem sepsis in sick patients in intensive care, is also commonly found in many organs during small bowel allograft rejection.[40] Therefore, in any rejection or GVHD episode, evidence of systemic infection should be sought and appropriate antibiotic treatment given immediately. Confirmation of the source of the infection can be achieved by culturing the same organisms from the stomal output or faeces of the patient.

Human small bowel transplantation

The first human small bowel transplant was undertaken in 1964. By 1971 seven cases of human small bowel transplantation had been reported in the literature.[41] All failed, most due to technical deficiencies or acute rejection. One patient lived for 76 days, taking nutrition through the transplanted intestine for part of this time, before dying of systemic infection associated with rejection.[41]

These poor results, and the introduction of total parenteral nutrition in the early 1970s, meant that few further attempts at small bowel transplantation were made until after the introduction of cyclosporin with its potent selective immunosuppressive action on T lymphocytes. With this new agent available, further attempts at small bowel transplantation were undertaken in patients who had sustained severe complications on total parenteral nutrition, particularly hepatic failure.[15] Most patients still suffered irreversible acute rejection, but one child transplanted in Paris and an adult transplanted in Kiel, are still living and receiving all fluid and nutrition by the enteral route, now two and a half and three years after transplantation respectively.[14 16]

Three years ago the first successful liver/small bowel transplant was carried out by Grant *et al* in London, Ontario.[28] The patient only experienced one early rejection episode and is fit and well at present, taking a normal diet. Four further transplants have been performed in this series and three of the five patients are well with functioning grafts.[22] In May, 1990, Starzl carried out the first of a series of small bowel and small bowel/liver transplants using the new immunosuppressant FK506 which had previously been shown to be effective in liver transplantation. The early results of the series have been reported by Iwaki *et al*,[23] and all of these patients have achieved full enteral nutrition and still have functioning grafts. Since then, at least six more patients have received small bowel transplants in Starzl's series, and apart from one who died from GVHD all have achieved full enteral nutrition via the grafted small bowel and the grafts continue to function.[42] However, all of these patients underwent serious postoperative complications necessitating continued hospital stay for between four and eight months after transplantation.

Thus in the last two years there have been a number of successful small bowel transplants. Most have been associated with postoperative complications, often due to infection. However, the recipients were extremely ill patients, some of whom were in advanced stages of liver failure at the time of surgery. In some American centres transplantation is now being offered to patients before they develop life threatening complications of total parenteral nutrition, and a corresponding reduction in postoperative morbidity is anticipated. In Europe, intestinal transplantation should be considered as a therapeutic option for patients who are failing on total parenteral nutrition. The European Intestinal Transplant Study Group is interested to receive details of any patient who might be an appropriate candidate for transplantation. There are grounds for optimism for many of the people currently committed to permanent parenteral nutrition.

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Archives of Disease in Childhood 1992; **67**: 980

LETTERS TO THE EDITOR

Prostacyclin concentrations in haemolytic uraemic syndrome after acute shigellosis

Sir,—We read with interest the report of Alam and colleagues implicating prostacyclin (PGI$_2$) in the pathogenesis of haemolytic uraemic syndrome after acute shigellosis.[1] However, we were confused by the methodology that they used to establish the PGI$_2$ concentrations in the plasma from their patients.

The authors state their intention to measure PGI$_2$ by firstly incubating rabbit aortic rings with their patients' plasma, and then subsequently assaying 6-keto-PGF$_{1\alpha}$ in the incubation fluid, a method described by Moncada *et al*.[2] We have used a similar technique to investigate the role of PGI$_2$ in the pathogenesis of meningococcal shock, in which patients' serum was incubated with human umbilical vein endothelial cells.[3] Both of these methods have been established to assess endothelial PGI$_2$ production in vitro in response to exogenous stimuli, and not, as suggested in this paper, to measure the concentration of PGI$_2$ directly in serum or plasma.

The distinction between direct measurement of PGI$_2$ and the effect of these patient samples on PGI$_2$ production by aortic rings is important in determining the significance of the results presented by Alam *et al*. A depression of PGI$_2$ synthesis in vitro in response to plasmas from patients with haemolytic uraemic syndrome suggests that there is either a deficiency of a factor necessary for PGI$_2$ synthesis, or that there is a circulating inhibitor. We have recently suggested that the former mechanism is the most likely explanation for the observed decrease in PGI$_2$ production by endothelial cells when incubated with the sera from children with meningococcal shock.[3] It is interesting that the PGI$_2$ concentrations reported by Alam and colleagues took a long time to recover. We have observed a defect in the serum of patients with meningococcal shock persisting for days, and sometimes weeks before normal endothelial PGI$_2$ synthesis can be demonstrated (unpublished results).

The authors conclude that the diminished PGI$_2$ concentrations reported in their study may be occur as a result of endothelial damage by endotoxin. However, the majority of in vitro, animal and human studies, to date, show that endothelial PGI$_2$ synthesis is stimulated rather than diminished by endotoxin.[4 5] This may occur as a direct response to endotoxin or following the elaboration of cytokines such as tumour necrosis factor and interleukin-1.[5 6] It would therefore seem unlikely that the action of endotoxin alone could adequately explain the depression of PGI$_2$ concentrations observed in haemolytic uraemic syndrome associated with shigellosis.

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Diazoxide—an orphan drug?

Sir,—In the article on surgical treatment of hyperinsulinaemic hypoglycaemia in infancy and childhood the authors state that diazoxide, which inhibits glucose stimulated insulin secretion, is still the mainstay of medical management.[1] However, they fail to mention that, in its oral form, this drug is no longer readily available as the manufacture of this therapeutically desirable but commercially non-viable product has ceased and, thus, satisfies the definition of an orphan drug.[2]

This problem applies to other essential drugs and compounds used in paediatric practice, particularly for the treatment of inborn errors of metabolism. There is a clear need for the drug industry to be supported (by government subsidies if necessary) to maintain production of such essential drugs. Patients need orphan drugs and this must be the overriding consideration. Consequently, paediatricians, through the British Paediatric Association and the Royal Colleges should encourage the Department of Health to provide such direction to the drug industry, perhaps through the establishment of an orphan drug regulatory body under the auspices of the Medicine Control Agency.

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Archives of Disease in Childhood 1992; **67**: 981–984

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Dec 26 7/93

ARCHIVES OF
DISEASE IN
CHILDHOOD

The Journal of the British Paediatric Association

Annotations

Current status of definitive surgery for congenital heart disease

The past 30 years have witnessed major changes in surgical treatment of congenital heart disease (CHD). The early years of innovation have been superseded by a new era of scientific assessment enabling the surgeon and the cardiologist both to evaluate and develop therapeutic strategies for the different groups of patients with CHD.

In considering the current status of surgery for CHD one should be clear that modern surgical strategies may involve staged procedures in order to achieve a definitive long term outcome. Current treatment protocols therefore demand total integration of the services provided by surgeons, paediatricians, and cardiologists and this 'team approach' remains the cornerstone of any successful surgical programme.

The past decade has witnessed an increasing tendency to advocate 'definitive' operation where possible in neonatal or infant life. Thus, for instance, infants with ventricular septal defect and intractable cardiac failure can now undergo definitive surgical repair with a mortality approaching zero. In this brief review I will address the current status of 'definitive' surgery in this younger age group. In all instances, it must be remembered that growth of the patient will often necessitate some further surgical intervention, most commonly when artificial conduits are employed as part of the original reconstruction. The term definitive must therefore be used with caution and close cardiological supervision is mandatory for all patients who have undergone surgery for CHD in childhood.

Transposition of the great arteries (TGA)

Although it has been possible for many years to achieve good early results in surgery for TGA using an atrial correction in which systemic venous blood is directed by means of an intra-atrial baffle to the left ventricle and pulmonary artery (Senning or Mustard operation), the intermediate and long term results have revealed an unacceptable late morbidity.[1] [2] The arterial switch operation, in which the aorta and pulmonary arteries are divided and retransposed to the anatomically normal position together with appropriate relocation of the coronary arteries, has thus become preferred treatment of choice for patients with TGA unless there is significant pulmonary or subpulmonary stenosis. Even when TGA is associated with other complex malformations, an arterial switch procedure should normally be undertaken at the time of repair of the associated cardiac or extra cardiac anomalies.

Planche *et al* recorded a hospital mortality of 8·3% in neonates,[3] similar to that reported by Brawn *et al* for this group of patients.[4] With increasing experience, particularly in the management of variations in coronary artery anatomy, the current hospital mortality for patients with TGA and intact ventricular septum at our institution is 1·8%, while that of complex TGA, primarily determined by the nature of the associated lesions, is 5·5%. Most recently, increasing confidence in the arterial switch procedure has led to its application in more complex forms of transposition, for instance those associated with atresia of a single atrioventricular valve, in an attempt to avert the morbidity often previously seen after palliative procedures such as pulmonary artery banding.

Although follow up of patients in most series is relatively short, it appears that the main postoperative problem in patients undergoing an arterial switch repair is the development of pulmonary artery stenosis. This occurs, in our experience, in 10% of patients and may be treated successfully in most cases by catheter balloon dilatation of the obstruction.

In older patients in whom right ventricular dysfunction has developed many years after a previous Senning or Mustard operation, the arterial switch procedure may still be applicable. Before such an operation, however, the left ventricle must be conditioned to develop systemic levels of blood pressure and this may be achieved by pulmonary artery banding. At present the mortality and morbidity of this staged approach remains high.[5]

Atrioventricular septal defect

While partial atrioventricular septal defect may be treated in a similar way to atrial septal defect (repair before school age), the treatment of complete atrioventricular septal defect poses a major surgical challenge. The risk of obstructive pulmonary vascular disease secondary to pulmonary hypertension is such that primary repair within the first year of life is advocated by most major centres. Current experience suggests that a hospital mortality of 3–10% should be expected.[6] [7] The reoperation rate, usually for residual ventricular septal defect or left atrioventricular valve incompetence is between 8 and 16%. These results are encourging when compared with the 20% mortality published in series prior to 1983.

Tetralogy of Fallot

Controversy still remains over the optimal timing for definitive surgery in tetralogy of Fallot.[8] Both proponents of complete repair in infancy and two stage repair (initial shunt formation followed by later correction) cite a hospital mortality well below 5% with similarly low figures for late mortality. On the other hand, repair in early infancy is undoubtedly associated with a higher incidence of patch enlargement of the right ventricular outflow tract extending across the pulmonary valve annulus. This inevitably produces some degree of pulmonary valve incompetence. The long term sequelae of mild or moderate pulmonary incompetence do not appear to be troublesome at up to 20 years after repair of tetralogy of Fallot. However, the natural history of congenital isolated pulmonary valve incompetence would suggest that important right ventricular dysfunction may be expected after 20–30 years[9] and this may be especially true when surgical repair has been performed through a right ventriculotomy incision. It is possible therefore that we may expect to see an increase in the number of young adults who have undergone repair of tetralogy of Fallot and who require later pulmonary valve insertion. Once again this emphasises the importance of adequate long term cardiological follow up of these patients.

Pulmonary atresia

Pulmonary atresia whether with intact ventricular septum or ventricular septal defect remains a difficult management problem. In patients with pulmonary atresia and intact ventricular septum initial palliation, usually by placement of a patch across the right ventricular outflow or systemic to pulmonary artery shunting, may permit later operative correction resulting in a heart with normal anatomical relationships. In many patients, however, a palliative atriopulmonary connection will remain the only definitive treatment option in the longer term When pulmonary atresia is associated with ventricular septal defect, the pulmonary blood supply may originate in large part from abnormal major aortopulmonary collateral arteries (MAPCAs). In this situation definitive repair demands initial palliative procedures in which these abnormal MAPCAs are anastomosed together prior to a final biventricular corrective repair. Although the mortality and morbidity of these procedures has been high in the past, current experience suggests that excellent results can be achieved in this difficult group of patients provided they are entered into an appropriate surgical programme early in the course of their disease.[10–12]

Aortic arch anomalies and aortic coarctation

Surgical repair of aortic coarctation is now well established whether this condition presents in neonatal life or beyond. Current experience suggests that, while balloon aortic dilatation may be applied to certain types of native aortic coarctation, the major role of this treatment lies in the treatment of aortic recoarctation. Present concepts favour concomitant primary repair of aortic arch anomalies such as interrupted aortic arch, usually by end to end anastomosis of the affected segments, and the associated intracardiac defects at the time of initial presentation. The hospital mortality in these complex cases still remains high however (10–20%)[13] and residual aortic narrowing or recoarctation will often require treatment by angioplasty.

Aortic valve stenosis

This condition remains one of the more difficult management problems in the young patient. While most patients presenting with critical aortic stenosis will progress well after surgical valvotomy, the longer term outlook for some of these patients and for older patients with aortic valve disease remains uncertain. The morbidity attendant upon anticoagulation treatment in patients who undergo aortic valve replacement, with a mechanical prosthesis at a young age, detracts significantly from the merits of such operations. Experience with aortic homografts as valve substitutes in young children has been encouraging but these patients also face potentially hazardous reoperation as they grow older. More recently, the use of the pulmonary valve as an autograft aortic valve replacement has been recommended by Gerosa *et al* in the hope that this valve substitute will grow with the child and thereby minimise the longer term morbidity.[14] As yet, however, data on the growth of this valve substitute is available in only a very small number of patients and so the management of patients with aortic valve dysfunction remains problematical.

Conclusion

It will be clear from these observations on a few selected conditions that definitive surgery for congenital heart disease can be considered for most situations with the aim of achieving normal atrial, ventricular, and great arterial connections and relationships. The team approach to the problems posed by patients with congenital heart disease encourages us to look forward to the next decade with optimism as we seek to develop and evaluate the role of definitive surgery in the palliation of entities such as hypoplastic left heart syndrome and other conditions where restitution of normal cardiac relationships remains an impossibility.

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The molecular basis of nephrogenesis and congenital kidney disease

To the paediatrician, the kidney means disorders such as polycystic kidney disease, Wilms' tumour, congenital malformations, and nephrotic syndrome. To the developmental biologist, on the other hand, the kidney is important as a developmental model, partly because of the richness of its organisation and partly because, unusually for a mammalian tissue, much of its morphogenesis will take place in vitro. In the past, paediatric nephrologists and developmental biologists have not had much to say to one another, but, as kidney disorders with a genetic component are helping to illuminate the molecular basis of nephrogenesis and as it is becoming clear how the study of normal development can explain congenital kidney disease, their interests are converging and they have the techniques of molecular genetics to thank for this.

Such an approach to the study of nephrogenesis is relatively recent, but three lines of work are already under way. These are the searching of cDNA libraries coupled with *in situ* hybridisation to identity, characterise, and localise molecules expressed during normal and abnormal nephrogenesis, experimentation on cultured kidneys to investigate the role of these molecules, and the manufacture of transgenic mice with defective expression to show how development proceeds in their absence. Although there is a great deal more to come, enough is now known to illuminate something of the relationship between the molecular basis of normal development and the origins of congenital kidney disorders.

Normal development

Metanephric development in mammals begins soon after the hind limbs start to form when a small epithelial bud off the Wolffian duct invades a domain of dense metanephric mesenchyme (the metanephric blastoma). A reciprocal induction then takes place between the two and the bud extends and bifurcates to form the ureter and the collecting ducts, while the mesenchyme, under the influence of the nerves associated with the bud, differentiates into nephrons.[1–3] This is a prolonged process with the outer part of the mesenchyme initially remaining as stem cells, while the inner cells rapidly associate into small aggregates. Each of these then epithelialises and undergoes the complex elongations and convolutions that lead to the formation of a nephron, with the one end fusing to a duct and the other interacting with capillaries and forming the renal capsule.[4] Meanwhile, as these ducts extend, more of the peripheral stem cells enter the nephron pathway and then more, so that, in humans, some six tiers of nephrons form. As to development in vitro, an uninduced mouse rudiment will form a complex ducting system having perhaps 35 nephrons with glomeruli[5] (albeit incomplete).

Some effort is being put into identifying genes that have a direct role in kidney function and how diseases like Alport's can arise if molecules such as collagen IV are aberrant.[6] The main line of contemporary research, however, is in elucidating the molecular controls underpinning kidney development and, here, it is known that many of the transcription factors.[7 8] growth factors,[9] and oncogenes[10] involved in controlling gene expression throughout the embryo are expressed during nephrogenesis.[11] In most cases, the functions of these molecules remains obscure, but experiments in which kidney rudiments are cultured in the presence of antisense oligonucleotides that block the transciption of the corresponding mRNA[12] may clarify their roles.

Kidney disorders

CONGENITAL MALFORMATIONS

Nephrogenesis is complicated, and it is one of the unstated marvels of development that the mature kidney is almost always normal. Nevertheless, things can easily go wrong that result in congenital malformations.[13] If, for example, growth is slow or the regulation of stem cells goes awry, a small or hypoplastic kidney will result. If the two ureteric buds become so close that their respective mesenchymes interact (and they are only about 1–200 µm apart when they first form in the mouse embryo), the resulting fusion will give rise to horseshoe kidneys. Such congenital disorders may be of medical concern, but experimental research will only be worth doing in cases where this is a clear heritable disorder or if there is a good animal model with which to work.

WILMS' TUMOUR

For these reasons, attention is now being focused on those diseases accessible to such analysis and the paradigm here is Wilm's tumour, a nephroblastoma where the control of stem cell differentiation is lost and whose aetiology involves a strong genetic component.[14] Detailed analysis has now shown that the disease sometimes involves a molecule known as WT1 with at least two more being expected, one of which is associated with the Beckwith-Wiedmann syndrome and is at the 11p15.5 locus[15] where it shows strong evidence of imprinting together with tight linking to the IGF-2 site.[14] WT1 is sited on the short arm of chromosome 11 at the 11p13 locus, is expressed in four alternative splice forms and its absence or mutation can lead to uncontrolled stem cell proliferation. Its genetics is, however, complex. In Wilms' tumour and the Wilms', Aniridia, Genital abnormalities, and mental Retardation (WAGR) syndrome, the WT1 locus is recessive and thus acts as a *tumour suppressor*,[16 17] in the Drash syndrome which is characterised by Wilms' tumour, pseudohermaphroditism, and renal failure the mutation is however dominant.[18] Although we cannot yet explain this difference, these diseases do point to WT1 having an important role in the development of the urinogenital system.

The WT1 gene encodes a large protein with four zinc fingers that seem to bind to several DNA sequences controlling the expression of molecules likely to be involved in nephrogenesis.[19] In the developing kidney WT1 is expressed in the uninduced stem cells, the early nephrons, and the glomeruli. Elsewhere it is present, *inter alia*, in the gonads, in several sites at which mesenchyme is making the transition to epithelium[20] and in Wilms' tumour.[21] To summarise our current view, it seems that WT1 is a transcription factor present in large amounts in induced metanephric mesenchyme and whose zinc finger site binds to several activation sites, so stimulating the cascade of the events that allows nephrogenesis to take place. In this context, it is not surprising that mutations in WT1 lead to aberrant induction and hence to cancer.

POLYCYSTIC KIDNEY DISEASES (PKD)

Perhaps the most important developmental disorder of kidneys, however, is the formation of cysts in the collecting ducts. Of the various types known, the most interesting academically is multicystic dysplasia: here, cysts appear during embryogenesis while nephrons fail to form due to a breakdown in induction.[4, 22, 23] We do not yet have an exact animal analogue for this disease, but the C57BL/6J-*cpk* mouse is a good model for autosomal recessive PKD in which cysts also develop during embryongenesis. In this mouse, SGP-2, a cell-surface glycoprotein involved in epithelial development, is up-regulated in the cysts[24] and its presence there suggests that cyst formation arises from incomplete duct differentiation. This view is strengthened by the facts that *c-myc* and other oncogenes, normally present only during nephrogenesis, are also expressed in the kidneys of this mouse.[25]

The other inherited form of PKD is an autosomal dominant disease (ADPKD) which is characterised by the slow development of cysts. There is now a mouse that develops cysts over a relatively long period[26] and hence is a model for this disease; the lesion here has, however, yet to be elucidated. Some intriguing evidence that the two forms of PKD may in some way be related is now being provided by a transgenic mouse which constitutively produces *c-myc* and develops ADPKD,[27] although the dominant effect probably derives from the nature of the extra control genes in the transgenic mouse.

The future

Because of the importance of WT1 in both normal and abnormal development, substantial effort is being devoted to working out its function. This involves looking for DNA sites to which WT1 can bind, culturing kidneys in the presence of antisense oligonucleotides to WT1, trying to elucidate the roles of the various splice forms, and making transgenic mice in which WT1 expression is suppressed. Together, these approaches should tell us a great deal about both normal nephrogenesis and the initiation of kidney and perhaps other cancers.

The use of trangenic mice to investigate Wilms' tumour is, it should be said, part of a major biomedical trend that is reflected in other areas of kidney research and, in addition to those already mentioned, such mice are being used to study renin production[28] and nephrotic syndrome.[29] These are thus exciting times for kidney research and, such is the rate of progress in this field, it should not be too long before we know a lot more about the molecular basis of congenital and other kidney diseases.

The author thanks the National Kidney Research fund for their support

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Archives of Disease in Childhood 1992; 67: 985–993

ORIGINAL ARTICLES

Haemorrhagic shock encephalopathy syndrome in the British Isles

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Abstract

The aetiopathogenesis of haemorrhagic shock encephalopathy syndrome (HSES) remains unclear and after concern that a novel environmental agent was the cause, the British Paediatric Association and the Public Health Laboratory Service Communicable Disease Surveillance Centre in 1983 initiated surveillance of this condition in the British Isles. After 1986 cases were ascertained via the British Paediatric Surveillance Unit 'active' reporting scheme; this report presents the findings for 1985–8.

Sixty five patients were reported, of whom 52 satisfied the criteria for inclusion. Of those whose outcome was known, 24 (46%) died, 18 had severe neurological damage, and six survived apparently intact. Epidemiological features of note were: the median age of 15 weeks (range 3–140); statistically significant clustering of admission times suggesting a peak onset period at night; lack of geographic clusters, of secular trends and, except for a slight excess in winter months, of seasonality.

Clinical and pathological features followed a highly consistent pattern, suggesting that HSES is an individual clinical entity distinguishable from conditions with similar presentations, such as septicaemia and Reye's syndrome.

There was no microbiological or epidemiological evidence to support the emergence of a novel environmental agent. Many of the features of HSES were, however, the same as those described in heat stroke and we suggest that the two conditions are the same even though there is usually no history of overt overheating.

(*Arch Dis Child* 1992;67:985–993)

Haemorrhagic shock encephalopathy syndrome (HSES) is a rare but devastating disorder of young children. It was first presented as a clinical entity under this name by Levin *et al* who in 1983 described 10 cases in the UK,[1] although series from France and England describing patients with a similar constellation of clinical features had appeared earlier.[2 3] Subsequently, over a hundred cases of HSES have been reported in the world literature: from the Netherlands,[4] Spain,[5] Belgium,[6] France,[7] Germany,[8 9] Portugal,[10] New Zealand,[11] Israel,[12] the United States,[13–18] the Far East,[19 20] and further cases in the UK.[21–26]

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Accepted 10 April 1992

After concerns that HSES might be a new disease caused by a novel environmental agent,[1] the Public Health Laboratory Service Communicable Disease Surveillance Centre (CDSC) and the British Paediatric Association (BPA) set up a joint surveillance scheme in the British Isles. The results for 1982–4 have been reported[26] and we now present the findings for 1985–8, after which surveillance was discontinued. During this second period information was collected in greater detail so that the features of HSES could be delinated more fully, with the object of assisting the diagnosis and elucidating the aetiopathogenesis.

Methods

CASE DEFINITION

Clinicians were given the following guidelines but were asked to report even if all nine criteria were not met. A child had to be under 16 years of age with acute onset of: (1) encephalopathy, (2) shock, (3) disseminated intravascular coagulation, (4) diarrhoea (may be bloody), (5) falling haemoglobin concentration and platelet counts, (6) acidosis, (7) raised hepatocellular enzymes, (8) renal function impairment, and (9) negative cultures of blood and cerebrospinal fluid.

The criterion that plasma ammonia concentration should be normal, used in the 1982–4 reports, had proved inconsistent[26] so was discontinued for 1985–8.

For the analysis, patients were allocated to one of three groups:

(A) *Definite HSES*: all nine criteria satisfied.

(B) *Probable HSES*: either: (i) eight criteria satisfied but one not met or (ii) at least seven criteria satisfied but no information on the remainder.

(C) *Indeterminate/not HSES*: either: (i) insufficient information, or (ii) another diagnosis more likely, or (iii) presence of a preceding event which may have distorted the clinical course.

CASE ASCERTAINMENT AND DATA COLLECTION

Between January 1985 and May 1986, cases were ascertained through 'passive' reporting by paediatricians throughout the British Isles as described previously.[26] From June 1986 to December 1988, reporting changed to the 'active' system of the British Paediatric Surveillance Unit (BPSU).[27] The initial report generated a request to review case notes both from the first hospital and, where appropriate, from the referral centre. Epidemiological, clinical, and laboratory data were transcribed on to a standard proforma.

Results

A total of 65 patients was reported. Thirty two were classified as group A (definite HSES) and 20 as group B (probable HSES). The remaining 13 (group C) consisted of: (i) insufficient information (two cases); (ii) alternative diagnosis (three cases: septicaemia, toxic shock syndrome, valproate toxicity) and (iii) preceding event (eight cases: head injury, severe dehydration, laparotomy, adenotonsillectomy, severe hypoglycaemia, respiratory arrest, cardiac arrest (two cases)).

The following analyses include only the 52 group A and B cases.

EPIDEMIOLOGICAL FEATURES

The secular trends were unremarkable: there were 11 cases in 1985 (some of whom were described in another series[24]); seven in 1986, 18 in 1987, and 15 in 1988. The annual totals for the preceding three years had been 13, 22, and nine.[26] Small numbers hamper interpretation of seasonality, but there were no clear trends either within each year or taking the period as a whole. However 29/52 (56%) of the cases occurred in the winter quarters (the same proportion as in the 1982–4 cases) with the highest numbers occurring in January and February (eight and nine respectively).

As in the previous years, cases were reported throughout the British Isles with no obvious clustering in place or time. Eighteen of the 52 patients were referred to a tertiary care centre. The remainder were managed in their local district general hospitals.

The age range was 6 to 140 weeks (median 14·5) for group A and 3 to 86 (median 16) for group B. The mean age (SD) of the 52 cases as a whole was 19·3 (21·1) weeks and the median and mode 15 weeks and 13 weeks respectively. Fifty (96%) patients were under 1 year of age. The male:female ratio was 14:18 for group A and 13:7 for group B.

CLINICAL FEATURES (TABLE 1)

The 52 patients in groups A and B were clinically very similar and are considered together except where specified. Seven (13%) had pre-existing developmental anomalies and other problems: of these, two aged 13 and 17 weeks, had had repairs of cleft lip and palate, while a third aged 13 weeks had had a repair of a meningomyelocele; two others aged 48 and 36 weeks had spasticity and two aged 140 and 28 weeks had generalised delay. The mean (SD) age of the latter four babies was 63 (52) compared with 16 (12) weeks for the other 48 patients.

Table 1 Clinical features. Results are number (%)

	Group A (n=32)	*Group B (n=20)*	*Combined (n=52)*
Abrupt onset	32 (100)	20 (100)	52 (100)
Prodromal illness	19 (59)	12 (60)	31 (60)
Admission temperature >40°C	18 (56)	9 (45)	27 (52)
Circulatory collapse	32 (100)	20 (100)	52 (100)
Coma	24 (75)	15 (75)	39 (75)
Convulsions	32 (100)	18 (90)	50 (96)
Respiratory disturbance	30 (94)	18 (90)	48 (92)
Vomiting	7 (22)	5 (25)	12 (23)
Loose stools	32 (100)	17 (85)	49 (94)
Oliguria/anuria	27 (84)	15 (75)	42 (81)
Manifest bleeding tendency	27 (84)*	15 (75)*	42 (81)*
Liver enlargement	22 (69)	13 (65)	35 (67)
Outcome:			
Full recovery	4 (13)	2 (10)	13 (2)
Death	13 (41)	11 (55)	24 (46)
Neurological damage	14 (44)	4 (20)	18 (35)
Uncertain	1 (3)	3 (15)	4 (8)

*Five further cases in group A and two in group B had abnormal coagulation tests

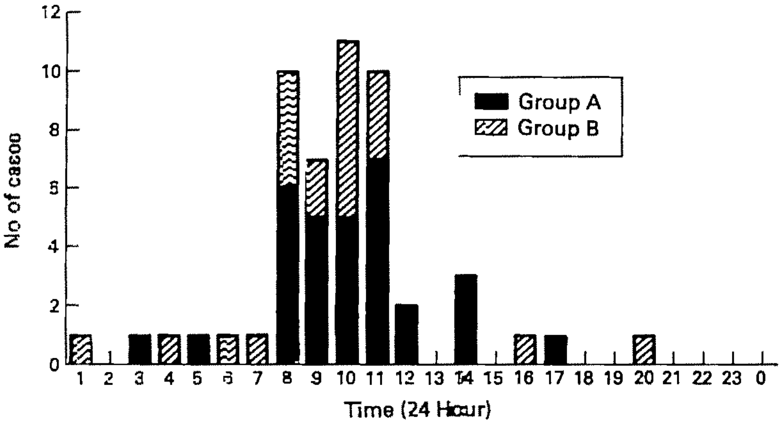
Thirty one patients had a mild prodromal illness with respiratory (n=19) or gastrointestinal (n=12) symptoms. The remainder had been well, although five had had recent contact with infection.

Three babies were each one of twins. In two of these cases (reported in detail elsewhere[25]) the other twin was found dead at the same time, the deaths being attributed to sudden infant death syndrome (SIDS).

The onset of the main illness was invariably abrupt and catastrophic. Although all the babies had been well or only mildly unwell when last seen (usually the previous night) most were found extremely ill in their cots first thing next morning; this characteristic timing was reflected in the clustering of admissions between 8 am and 11 am (figure); this clustering was unlikely to have occurred by chance ($\chi^2=75{\cdot}24$, 5 df $p<0{\cdot}001$).

All 20 babies whose condition when first found by the parents was recorded, were described as unusually hot or sweaty. The first recorded temperatures, taken at varying intervals after admission (methods varied and were inconsistently reported), indicated that most babies (42/49 with this information) were febrile. The modal temperature was 40–41°C and seven patients had a temperature ≥42°C. Six had subnormal temperatures, one as low as 27°C, but all had been stripped for some time before the recording. One baby had a normal temperature.

No patient was reported to have a rash. Conscious level on admission was recorded in 51 cases: 39 were comatose, 24 dying without regaining consciousness. The other 12 were semiconscious or poorly responsive. Fifty babies had convulsions of whom 35 (67%) were fitting on admission and 10 more began to fit within a few hours. Convulsions were usually generalised or multifocal and difficult to control, especially if they had started early. Of the two babies in



Time of admission to first hospital in HSES (n=51, one baby not known).

whom no fits were recorded, one died soon after admission and the other had been promptly paralysed for ventilation.

Vomiting was not a major feature; it occurred in only 12 cases and was not copious. Loose stools were noted in all cases except three, either at admission or within the next 10 hours; usually profuse, they were also bloody in 19 cases (37%). Twenty one babies (40%) were assessed as dehydrated on admission, one severely so. Circulatory collapse ('shock') was present in all cases. The mean systolic blood pressure on admission, measured in 32 cases, was 58 mm Hg (range 0–99 mm Hg) and the mean pulse rate, 177/minute (range 110–250/minute). Progressive hepatomegaly, defined as a liver edge more than 2 cm below the costal margin, was recorded in two thirds of cases, reaching a maximum at about 24 hours, with the liver extending usually about 4 cm, but in one case 9 cm, below the costal margin.

Forty two babies (81%) had anuria or oliguria. When urine was passed it usually contained protein and red blood cells. Three babies were dialysed and six others died anuric. In the 10 cases where oliguria was not documented the blood urea concentration was nevertheless raised.

Most babies had disturbed breathing patterns when first seen, respiration usually being rapid and shallow (n=36) or sometimes very irregular (n=12). There was no evidence of major pulmonary disorder and the respiratory disturbances appeared to be central. Thirty nine babies (75%) required assisted ventilation, which was initiated sometimes for respiratory support and sometimes to control seizures and raised intracranial pressure. Ventilation was continued in some cases for up to seven days.

Forty two (81%) babies demonstrated a bleeding tendency within the first 24 hours of admission, usually from the gastrointestinal tract, venepuncture sites, or an endotracheal tube. Among the remaining 10 patients, clotting tests were abnormal in the seven in whom they were performed.

OUTCOME

Twenty four babies died (46%, 13 boys and 11 girls), 13 (41%) in group A and 11 (55%) in group B. Some died within a few hours of admission and 19 (37%) had succumbed by the fourth day of the illness. Death within 48 hours was more common in group B (eight cases compared with two in group A) possibly because it prevented the emergence of all the diagnostic criteria. Outcome was related to severity of encephalopathy at presentation: babies with intractable convulsions and deep coma were likely to die, while those with less depressed consciousness and less frequent fits usually survived.

Table 2 Laboratory results

	Group A (n=32)	*No of cases investigated*	*Group B (n=20)*	*No of cases investigated*
	Mean (SD)		*Mean (SD)*	
Fall in haemoglobin (g/l)	35·0 (16)	32	33·0 (11·0)	16
Lowest platelet count ($\times10^9$/l)	53·00 (24·7)	32	56·00 (26·00)	12
Initial white cell count ($\times10^9$/l)	22·90 (11·1)	31	24·50 (12·40)	20
Initial sodium (mmol/l)	145·00 (4·9)	31	146·00 (5·50)*	18
Initial bicarbonate (mmol/l)	11·50 (2·5)	31	11·40 (2·70)	17
Initial pH	7·16 (0·14)	26	7·12 (0·16)	15
Maximum blood urea (mmol/l)	17·00 (4·9)	32	16·20 (4·40)	16
	No of cases		*No of cases*	
Blood glucose <2 mmol/l	23	29	13	19
Hepatic transaminases: abnormal	32	32	18	18
α_1-Antitrypsin <20 µmol/l	5	12	1	7
Ammonia ≥100 µmol/l	9	29	5	16

*Excluding one concentration of 122 mmol/l

Of the 28 survivors, 18 had severe neurological damage, typically manifested by a fall-off in head growth, developmental regression, spasticity, cortical visual impairment, and seizures. In four babies the neurological outcome was uncertain, while six were deemed to have recovered. The mean duration of admission among survivors (excluding one child who stayed in hospital for seven months partly for social reasons) was 23 days (range 8–80 days). Early readmissions because of seizures were common.

HAEMATOLOGICAL FEATURES (TABLE 2)

Haemoglobin concentrations were normal at presentation in all patients, but in 47 of the 48 cases where successive measurements were made, fell by a mean of 36 g/l (range 17–83 g/l) over the next 12–48 hours. Eighteen babies received a blood transfusion. Platelet counts were initially always normal or raised, but fell to a mean of approximately 54×10^9/l (minimum 16×10^9/l) over a similar period. The initial white cell count was raised in every case except one, with a mean value of 23×10^9/l (range 7·3–67·3 $\times10^9$/l). Either neutrophils or lymphocytes were reported to predominate, and in some cases neutrophils were immature. Coagulation tests, a wide variety of which were performed in all except four patients, were always abnormal, with an initially moderate disturbance becoming more severe by 24 hours.

BIOCHEMICAL FEATURES (TABLE 2)

All patients except two were initially hypernatraemic, with a mean serum sodium concentration of 145 mmol/l and a highest value of 156 mmol/l. All were acidotic, the mean serum bicarbonate being 11·5 mmol/l (minimum 6·9 mmol/l) and the mean arterial or capillary pH being 7·16 (minimum 6·80). Acidosis was often hard to correct. Blood urea was usually slightly raised on admission and always rose higher over the next 48 hours to a mean maximum concentration of 17·0 mmol/l, the highest level being 29·7 mmol/l.

A progressive rise in hepatocellular enzymes was invariable, activities being moderately raised where assays were done early and grossly raised by 48–72 hours. Hypoglycaemia (blood glucose <2 mmol/l) was a common early feature, being recorded in 36 (75%) of the 48 cases in whom the blood glucose was measured (this includes some measurements by reagent strips as well as laboratory assays). Hypoglycaemia was either present on admission (14 cases, 29%) or developed over the next few hours (22 cases, 46%). It was often profound, with recordings of zero in 14 cases, and difficult to correct by dextrose infusion. No insulin assays were performed.

Plasma ammonia concentrations were measured at least once in 45 children, 29 in group A and 16 in group B. Thirteen patients had concentrations below 50 μmol/l, 18 between 50 and 99 μmol/l, and 14 had concentrations of 100 μmol/l or more, the highest being 328 μmol/l. In eight of the cases where the ammonia was 100 μmol/l or more, the sample had been taken within an hour of admission; in each of these eight the concentration had fallen below 100 μ/l within 24 hours. In five cases the timing of the raised concentration was not recorded; in one case it was recorded as normal on admission, but as 124 μmol/l 36 hours later.

α_1-Antitrypsin concentrations were available in 19 patients and were reduced (<20 μmol/l) in six, including all three in whom samples were taken in the first 12 hours. Only three recordings of immunereactive trypsin were available, all taken after 24 hours: two were normal and one appreciably raised (>400 mg/ml). Pi phenotyping was available on four surviving babies; three were Pi MM and one Pi MZ. Creatine phosphokinase was raised (1886, 1921, and 4185 IU/l) in three of the four cases in whom it was assayed, the samples being taken between 24 and 72 hours after admission. Amylase was assayed in five cases (all within 24 hours of admission); it was raised in one (240 IU/l) and normal in the remainder (68, 78, 131, and 163 IU/l).

Table 3 Microbiological findings

	Group A (n=32)	*Group B (n=20)*	*Combined (n=52)*
Blood culture			
Performed	32	18	50
Positive	7	8	15*
CSF culture			
Performed	32	16	48
Positive	2	0	2†
Stool culture (bacterial)			
Performed	32	19	51
Positive	4	2	6‡
Viral studies (culture or serology)			
Performed	23	12	35
Positive	5	1	6§

*Staphylococcus coagulase negative (n=10), Staphylococcus coagulase positive (n=2), *Streptococcus faecalis* (n=1), *Streptococcus viridans* (n=1), *Moraxella catarrhalis* (n=1)

†Staphylococcus coagulase negative (n=1), Staphylococcus coagulase positive (on enrichment) (n=1)

‡*Clostridium difficile* (n=3) pathogenic *Escherichia coli* (n=2), Gram positive cocci (n=1)

§Enterovirus (three including one coxsackie B5), adenovirus (n=1), rotavirus (n=1); parainfluenzae type 3 (n=1).

MICROBIOLOGICAL FINDINGS (TABLE 3)

Microbiological findings were inconsistent and of uncertain clinical relevance. The organisms grown from blood and cerebrospinal fluid (CSF) (15 cases and two cases respectively) were all regarded as contaminants by the clinicians concerned. No pleocytosis accompanied the two positive CSF cultures. However, in six other samples of CSF there was a small excess of lymphocytes, 7–16 cells being counted per mm^3. In 12 CSF samples the protein content was slightly raised, with a mean value (SD) of 79 (41) g/l.

Stool specimens were cultured in 51 cases, of which six yielded possible pathogens. No significant infection was found in the 46 patients whose urine was cultured.

RADIOLOGICAL FINDINGS

Chest *x* ray films were taken on 44 babies, usually after intubation. Abnormalities were seen in 15: collapse of an upper lobe (10 cases), streaky shadowing (two cases), underinflation of one lung (one case), aspiration (one case), and unspecified changes (one case). These appearances were thought by the relevant clinicians to be secondary rather than causative features of the illness.

NEUROLOGICAL INVESTIGATIONS (TABLE 4)

Electroencephalographic abnormalities of various kinds were found, focal or multifocal spike activity being the most common. Recordings made in the first 72 hours were abnormal in 22 of 23 patients; when 12 of these 22 were reexamined after an interval of a week or more, nine remained abnormal. Cranial ultrasonography was abnormal in 10 of the 24 patients investigated, with initial diminution of ventricular volume and subsequent asymmetry or atrophy of cerebral tissue. Computed tomography often showed diminution of ventricular volume initially and cerebral atrophy later; low density areas in the cortex were seen at all stages.

Table 4 Neurological investigations

Time after presentation	*Electroencephalography*		*Cranial ultrasonography*		*Cranial computed tomography*	
Total patients investigated 0–72 hours		23		17		10
	Focal/multifocal spikes	14	Diminished ventricles	7	Diminished ventricles	6
	Low amplitude activity	4	Normal	10	Low density areas	3
	Slow waves	3			Normal	3
	Flat	3				
	Unspecified abnormalities	5				
	Normal	1				
Total patients investigated 3–7 days		6		4		2
	Low amplitude activity	2	Asymmetrical ventricles	1	Diminished ventricles	1
	Flat	1	Normal	3	Low density areas	1
	Unspecified abnormalities	3				
Total patients investigated 8–120 days		12		3		7
	Focal/multifocal spikes	5	Asymmetrical ventricles	1	Low density areas	3
	Slow waves	1	Cerebral atrophy	1	Cerebral atorphy	4
	Hypsarrhythmia	1	Normal	1		
	Unspecified abnormalities	2				
	Normal	3				

Table 5 Postmortem findings

Case No	Duration of illness (hours)	Brain		Lungs		Liver		Kidneys		Adrenals	
		Gross	*Histology*	*Gross*	*Histology*	*Gross*	*Histology*	*Gross*	*Histology*	*Gross*	*Histology*
Group A											
1*	102	Soft and swollen, herniation	NA	Congestion, patchy haemorrhage	Focal haemorrhage	Fatty, 'nutmeg' pattern	CLN	Congestion	Some ATN	Normal	Medullary congestion
2	71	Swollen	Zonal hypoxic damage	Congestion	NA	Normal	NA	Congestion	NA	Normal	NA
3	19	Soft and swollen	NA	Congestion	NA	Pale	NA	Normal	NA	Normal	NA
4	65	Swollen	NA	Congestion, patchy collapse	Oedema	Slightly pale and fatty	CLN, some fatty change	Swollen	Normal	Normal	NA
5	51	Soft and swollen	NA	Congestion, patchy haemorrhage	Congestion, intra-alveolar haemorrhage	Enlarged and fatty	CLN	Normal	ATN possible chronic glomerulopathy	Normal	NA
6	52	NA	NA	Congestion	Focal haemorrhage	Not enlarged, mottled red/brown	CLN	Focal pallor	Some ATN	Some haemorrhage	Haemorrhage
7	56	Swollen, herniation	Hypoxic damage	Congestion	Congestion, focal haemorrhage	Enlarged irregular pale areas	Fatty change (microvesicular), focal necrosis (not zonal)	Normal	Normal	Normal	Normal
8	76	Swollen, herniation	Oedema	Congestion	Congestion	Normal	Periportal fatty change	Normal	Congestion	Normal	Normal
9	72	Soft	Hypoxic damage	Congestion, focal haemorrhage	Intra-alveolar haemorrhage	Enlarged and fatty	CLN, fatty change	Pale	Fatty infiltration of tubular epithelium	Normal	NA
10	29	Swollen, herniation	NA	Patchy collapse	Some oedema, intra-alveolar haemorrhage	Pale and fatty	Diffuse fatty change (microvesicular)	Normal	A few cystic tubules	Normal	Normal
Group B											
1	35	Soft, ?infarction	Haemorrhagic changes	Congestion, haemorrhage	Congestion	Pale, mottled	Intersinusoidal haemorrhagic changes	Congestion	NA	Haemorrhage, infarction	Infarction
2	56	Swollen, herniation	NA	Normal	NA	Partly yellow discolouration	NA	Congestion	NA	Normal	NA
3†	7	Normal	NA	Congestion	NA	?Fatty change	NA	Normal	NA	NA	NA
4	8	Congestion, focal haemorrhage	Microthrombi, microinfarction	Focal haemorrhage, ?pneumonitis	Congestion	Congestion	Congestion, no fatty change	Normal	Congestion	Haemorrhage, infarction	Infarction
5	12	Normal	NA	Congestion, haemorrhage	Congestion	Normal	Congestion	Normal	Normal	Congestion	Congestion
6	120	Swollen	Focal lymphocytic infiltration	Patchy bronchopneumonia	Congestion	Yellow	Centrilobular congestion, cholestasis	Normal	Normal	Swollen, haemorrhage	Normal

*Also pituitary necrosis, †also haemorrhagic colitis.
ATN=acute tubular necrosis, CLN=centrilobular necrosis, NA=not available

The sequence of changes found in these three investigations suggests an intial and severe generalised cerebral disturbance leading on quickly to cerebral oedema, and then sometimes to infarction and atrophy. Further evidence for an extreme rise in intracranial pressure was provided by a case in which brain tissue was extruded through a monitoring catheter.

POSTMORTEM FINDINGS (TABLE 5)

Necropsy reports were available for 10 of the 13 fatal cases in group A and for six of the 11 fatal cases in group B. A seventh group B patient had an immediate postmortem liver biopsy, but no necropsy.

Small focal haemorrhages in many organs were a common feature. The lungs were usually congested, and often there was focal intra-alveolar haemorrhage. The kidneys were usually normal, though some degree of acute tubular necrosis was seen in three cases. Adrenal haemorrhage and infarction was noted in four cases, and in one case there was infarction of the pituitary gland.

In 13 cases the brain was soft and/or swollen and in five of these there was cerebellar herniation; the three babies whose brains were not swollen had all died early in the illness.

Changes in the small gut were reported in three cases: in one, a degree of villous blunting, in the second, partial villous atrophy with crypt abscess formation, and in the third, an increase in acute inflammatory cells. In one baby aged 3 weeks, the youngest in the series, the only abnormality was in the macroscopic appearance of the large bowel, which was described as 'consistent with haemorrhagic colitis'. In this patient shock and encephalopathy had preceded bloody diarrhoea and she met the criteria for inclusion in group A.

The hepatic findings are described below in some detail in view of the interest in distinguishing HSES from Reye's syndrome (see discussion).

The macroscopic appearance of the liver was described as normal in only three of the 16 cases. Among the remainder it was 'pale', 'yellow' and/or 'fatty' (n=11); 'congested' (n=1); 'mottled reddish-brown' (n=1). There were abnormalities in all 13 livers examined histologically. In five of these, all group A, fatty changes were described: in one, the fat occurred throughout the lobule, but was reported 'insufficient for Reye's syndrome'; in another it was a diffuse microvesicular infiltration 'in keeping with a Reye-like syndrome'; in the third it was described as an 'extreme degree of fatty change'; in the fourth it was periportal; in the last it was 'widespread with small and medium sized vesicles not displacing hepatocyte nuclei and not typical of Reye's syndrome'. In three of these five cases hepatic cell necrosis was also reported: centrilobular in two, widespread and focal in one.

Necrosis was also reported in three further group A cases: centrilobular in one; widespread ('therefore not Reye's') in another and as 'massive infarction leaving only periportal cell remnants' in the third.

Overall, of the nine patients who had survived more than 48 hours and whose livers were examined histologically, six showed necrosis, and four had concomitant fatty changes. Of the four who had survived less than 48 hours, none showed necrosis and one showed fatty change.

There was no relationship between plasma ammonia concentrations and hepatic fatty changes.

Electron microscopy of liver tissue was available for only one patient and showed poor cellular preservation, 'blown' mitochondria, lysosomes containing dense areas, but no other distinctive features.

Discussion

This series of cases of HSES, ascertained by routine surveillance, had certain advantages over series reported from referral centres: it enabled epidemiological trends to be assessed; it represented a wider spectrum of the condition because it was not limited to cases severe enough to merit referral; and it allowed the evolution of a rapidly developing illness to be described from its outset.

The data confirmed other reports that most patients with HSES are aged between 3 and 4 months.[1 4–25] It has been proposed by Chaves Carballo *et al* that HSES should not be diagnosed beyond the age of 1 year.[17] However, two of the patients, one in each group, were aged nearly 2 and nearly 3 years respectively, and older cases have also been described by others.[5 7 15 24 26 28]

The overall male excess and higher mortality among females in the previous survey[26] was not seen among the 1985–8 cases. As in the earlier series, however, there was neither a distinct seasonal pattern (apart from a slight excess of cases in the winter months) nor any obvious place-time clusters.

The high rate (13%) of previously existing developmental anomalies and problems in these patients was also observed in the 1982–4 series[26] and by Levin *et al*, who noted such disorders in seven of their 25 patients, including two with Down's syndrome.[24] Furthermore, four of the oldest five infants in the 1985–8 survey had neurodevelopmental problems. These observations are unexplained, but may represent reduced ability to respond to a harmful stimulus because of impairment either of intrinsic mechanisms or of protective behavioural responses.

A mild prodromal illness was frequently but not invariably reported. Information was incomplete, but at least three babies who had no prodrome had been immunised in the preceding 72 hours. Given the frequency with which such symptoms and events occur in infants, however, their significance in the pathogenesis of HSES is uncertain. Despite extensive investigation, no microbiological aetiological agents, including 'exotic' viruses, have been consistently isolated from patients with HSES.[1 24] Positive microbiological findings in the current series were varied and were considered to be either non-contributory or contaminants.

As in previous descriptions,[1 4–25] a high temperature was initially observed in most (86%) of the patients reported to this survey, 14% having an admission temperature over 42°C. By contrast some babies had subnormal temperatures, but all of these had been stripped for some time. One baby was described as 'very, very hot to the touch' when found by her parent and the temperature was 41·6°C on admission, but had fallen to 32°C 10 hours later. A similar decline in temperature from high pyrexia on arrival at a casualty department to hypothermia after transfer to an intensive care unit some hours later, has been observed by others.[16] These observations suggest that temperature control may be impaired in HSES (perhaps because of preceding pyrexial insult to the hypothalamus) and illustrate how a normal or low admission temperature could be compatible with preceding fever.

Reports from tertiary referral centres have described death or brain damage as the usual outcome of HSES.[17 24] Among the 52 cases in this unselected series, six (12%) were reported to have survived intact, though there is still the possibility that sequelae may have emerged after longer follow up.

It has been questioned whether HSES is a distinct clinicopathological entity in its own right, or whether it represents the final common pathway of several disorders with similar features.[29] Although there is no single clinical or pathological factor that is pathognomonic for HSES, the pattern of features found in the present series (the largest yet described) and in others[4–26] is markedly consistent.

HSES can therefore, we believe, be distinguished from other conditions that share some of its features. The main differential diagnoses are septicaemia, overwhelming viraemia, Reye's syndrome, haemolytic uraemic syndrome, staphylococcal toxic shock syndrome, and various inherited disorders.

The presenting features of high fever, shock, and leucocytosis usually (and reasonably) prompt a presumptive diagnosis of septicaemia. If blood cultures are not taken before antibiotic treatment is begun, it is then difficult to exclude this diagnosis as many of the features of HSES, such as disseminated intravascular coagulation and renal failure, could be attributed to it. HSES may, therefore, be misdiagnosed as septicaemia, through either failure to take cultures before treatment or disregard of negative reports. While tropical viruses such as dengue might cause confusion with HSES, no viral infection of temperate climates, however severe and overwhelming, causes the same constellation of features.

The combination of cerebral and hepatic disorder, especially when accompanied by hypoglycaemia and hyperammonaemia, inevitably suggests Reye's syndrome. Indeed some authors have suggested that HSES should not be diagnosed if one or both of these biochemical abnormalities are present.[17 24] However, Reye's syndrome differs from HSES in a number of clinical and pathological details.

In Reye's syndrome the onset of illness is usually slower, with vomiting a prominent feature, while diarrhoea (especially if bloody) and disseminated intravascular coagulation are unusual. Patients with typical Reye's syndrome are considerably older (median age 8–9 years[30]) than those with HSES; where cases in infancy have been described some may have been confused with HSES.

The hyperammonaemia found in several of the patients in the present series was not as pronounced as that typically found in Reye's syndrome and there was a rapid reversion towards normal concentrations. Hyperammonaemia may be a non-specific accompaniment of severe illness and, moreover, ammonia assays are not always reliable when undertaken by laboratories not performing them regularly. Hypoglycaemia is similarly non-specific: it was a more prominent feature in the 1985–8 cases than in some series[1 24] but has been reported by others.[5 7 16 23]

Hepatocellular enzymes are increased to a similar degree in both disorders, but liver histology, with experienced interpretation, should be distinctive. Fatty change is always present in the acute phase of Reye's syndrome, persists for about five days and is typically diffuse, with panlobular microvesicular infiltration of hepatocytes, retention of nuclear position, and no necrosis or inflammatory infiltrates.[30] Fatty change was reported in five of the 13 HSES patients whose livers were examined histologically, but in only one of these was it described as consistent with Reye's syndrome. The illness duration was less than five days in all of this group.

Although the hepatic histological changes in Reye's syndrome are also seen in some other conditions, ultrastructural changes appear to be pathognomonic.[30] There is little published information on hepatic ultrastructural changes in HSES.[7] Electron microscopic examination could be useful in distinguishing it from Reye's syndrome for those cases with fatty livers, but this is best undertaken on antemortem biospy material, which may limit the feasibility of this approach.

The combination of bloody diarrhoea, renal failure, and disseminated intravascular coagulation may lead to confusion with haemolytic uraemic syndrome. However, in haemolytic uraemic syndrome the onset of the condition is usually less abrupt, diarrhoea precedes rather than accompanies the main illness, encephalopathy, if present, comes late, and liver function is seldom disturbed.

Staphylococcal toxic shock syndrome presents with the same abruptness as HSES and shares the features of high fever, shock, and multisystem involvement. However, there is invariably a rash, not seen in HSES, and a focus of infection is usually evident (the scanty growth of staphylococci in three of our cases was attributed to contamination). Streptococcal toxic shock syndrome is a newly emerging entity which may not always be associated with a rash. It has mostly been described in adults and again there is usually an obvious focus of infection. Group A β haemolytic streptococci were not isolated from any of the patients with HSES.

Various genetic disorders such as malignant hyperpyrexia and inborn errors of metabolism including disorders of ketogenesis, urea cycle disorders, and organic acidurias may present with sudden onset of encephalopathy in infancy or childhood. However, except in malignant hyperpyrexia, high fever is not normally a presenting feature. There may be a suggestive family or personal history, which was not recorded for any of the patients with HSES in the current series (in contrast to the 1982–4 survey[26]) except the two whose twin died the same night.

The simultaneous occurrence of HSES and SIDS in the pairs of twins in this series supports speculation about a link between the two conditions.[11 25] Other features supporting such a link are a similar age range, the modal age for HSES coinciding with the second peak of the bimodal distribution for SIDS, and the slight excess in the winter months. Among babies who are classified as having had an 'acute life threatening event' there may be some who have in fact had HSES.

In the absence of an established cause for HSES, explanation of its pathological features remains speculative. We suggest that most (if not all) may best be explained as secondary phenomena following a severe initial insult that affected many tissues.

Various stimuli, not necessarily infective, may cause leucocytosis and also trigger disseminated intravascular coagulation, thereby producing a rapid fall in haemoglobin and platelets. The severe acidosis of HSES is mainly metabolic and may arise initially from poor tissue perfusion and then from renal failure.

Hypoglycaemia was an unexpected and interesting finding; it may have resulted from sudden hepatic dysfunction, but its refractoriness raises the possibility of hyperinsulinaemia. Unfortunately, no insulin assays were undertaken. Although no pancreatic damage was observed at postmortem examination, the increase of amylase and trypsin is compatible with a leak of pancreatic enzymes.

Hypernatraemia could be explained by sweating; it was found before the onset of diarrhoea, so that intestinal fluid loss is a less likely explanation. The peaking of hepatocellular enzymes at about 48 hours suggests an evolving disorder of hepatic cells that subsequently resolves. Creatine kinase and trypsin were most often found to be raised and α_1-antitrypsin to be depressed at the onset of the illness and then to revert to normal, suggesting that these were secondary rather than causative features.

Postmortem findings were generally non-specific and were all consistent with reduced blood flow and hypoxia secondary to hypotension. Cerebral oedema may result from a variety of insults, while acute renal tubular necrosis and hepatic centrilobular necrosis may both follow circulatory failure. Widespread petechial haemorrhages are commonly found in babies dying from SIDS and are also often found at postmortem examination when there has been hypoxic capillary endothelial damage while the circulation continues. Changes in small gut histology similar to those found in four of the cases have been associated with overheating in one report,[3] but were regarded as non-specific in another.[31]

Several authors have commented on the close similarity between the clinical and pathological features of HSES and those of heat stroke.[2 7 10 12 15 17 32 33] The most detailed descriptions of heat stroke are of soldiers in hot climates,[34 35] but there are also some of babies left in cars in the sun,[36 37] who appear to be affected in the same way as adults. Such patients present with acute encephalopathy (convulsions, altered consciousness), initial profuse sweating, shock, diarrhoea, renal failure, hypernatraemia, metabolic acidosis, clotting disturbance, thrombocytopenia, and raised hepatic transaminases. Illness severity may be determined not only by the thermal environment but also by individual susceptibility,[34] the nature of which is not yet understood.

Pathological features, also described in patients given hyperthermia therapy,[38] include cerebral oedema, characteristic changes in the dentate nucleus, Purkinje cells, and Bergmann astrocytes; hepatocellular necrosis and fatty change (both dependent on illness duration); and diffuse multiorgan petechial haemorrhages.

There have also been reports from France,[39] India,[40] and England[3] of infants and young children presenting with an illness identical to heat stroke, but lacking a clear cut history of overheating. The authors suggest that heat injury may nevertheless have been the cause if the effects of an initial febrile illness were compounded by excessive insulation (in the European cases) or by very high ambient temperature (in the Indian).

The similarity of these cases and of HSES to classical heat stroke supports the hypothesis that all these disorders may be one and the same. Biochemical abnormalities reported in HSES, but not in heat stroke, such as raised serum trypsin and reduced α_1-antitrypsin, may not yet have been sought in the latter condition. It is possible that they are among many epiphenomena that follow an initial global insult. To date there appear to have been no reports in HSES of the specific changes in brain histology noted in heat stroke; it is possible that they, too, have not been sought.

One group has reported finding botryoid nuclei in peripheral white blood cells (said to be specific for heat stroke) in two HSES patients on admission, but not 24 hours later.[10] They were not noted among any of the patients in the present series, but again were probably not specifically sought within the critical time period.

Other authors have expressed scepticism about the relationship between HSES and heat stroke, mainly because of the apparent absence either of a history of overheating or of a very high temperature on admission.[4 9 24 25 41] Admission temperature is, however, an unreliable indicator of preceding hyperpyrexia and specific details of the infant's home thermal environment are necessary to elicit the possibility of overheating.[42] These should include the temperature of the infant's bedroom, the insulation provided by the clothing and bedding (preferably estimated in tog values), whether the head was covered, and whether the baby was hot and sweaty when first found.

Other aetiopathogenic theories, for example that HSES results from deficiencies of protease inhibitors,[24] abnormalities in stress protein production,[25] or bacterial endotoxin leaking through a gut lining damaged by splanchnic ischaemia,[18] are all compatible with the notion that the pathogenic cascade of events culminating in HSES results from a heat induced trigger in a genetically determined, susceptible individual. The rarity of HSES could be compatible with this hypothesis, because an improbable combination of risk factors would have to be present to initiate the cascade. It would also explain the characteristic age range (a time of life when both thermoregulation is immature and maternally derived immunity is waning) and would be compatible with the occasional case occurring in older children—a similar pattern is seen in some of the infection-precipitated Reye-like metabolic disorders. The highly significant clustering of admission times (unlikely to be confounded by administrative factors in such severe illness) also supports this hypothesis—it suggests a peak onset period at night, a time when a baby may be most at risk from heat injury.[43] If HSES is, therefore, the result of heat injury, then it is not a new disease. However, recent fashions in bedroom heating and babies' bedding and clothing may pose new risk factors for the condition.

In the absence of a clear understanding of the aetiopathogenesis of HSES, management has to be non-specific and supportive. The current survey did not aim formally to evaluate treatment, which essentially is a salvage operation after the initial catastrophic event preceding presentation. The variety of measures used were dictated by the course of the illness. It was not possible to demonstrate that any had a consistent beneficial effect, although early vigorous measures to counter cerebral oedema appeared to be associated with improved outcome.

We agree with others, that the term 'haemorrhagic' shock is misleading, because it implies that shock ensues from haemorrhage, whereas in fact it precedes it.[44] As abrupt onset is invariable, we suggest that if a change of title is contemplated, 'acute shock encephalopathy syndrome' might be more appropriate. Alternatively, if the condition is indeed a form of heat stroke another title is unnecessary.

We propose that the diagnoses of HSES be made on the basis of the features specified in our case definition, plus the exclusion of the similar disorders discussed above. We do not agree that an upper age limit of 1 year should be set or that patients with hypoglycaemia and hyperammonaemia should be excluded. We further suggest that clinical and pathological observations in future series should be reported in relation to the interval after onset, and that there is a need for more detailed and systematic histological and ultrastructural studies, particularly of brain and liver.

In conclusion, the data from this CDSC/BPA surveillance scheme do not suggest that HSES was a major new and increasing public health problem in the British Isles in the 1980s, associated with some novel environmental agent. However, although the disease is uncommon it is so severe that further studies to elucidate its aetiopathogenesis are essential, especially as the possibility of a preventable cause, namely hyperthermia, has been raised.

We thank the paediatricians who reported cases and who gave permission to review case notes and include their patients in the surveillance scheme We wish to acknowledge Dr Jean Keeling for her helpful comments on the manuscript. We also thank the British Paediatric Surveillance Unit, which is generously supported by the Children Nationwide Medical Research Fund.

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Archives of Disease in Childhood 1992, 67: 994–997

Optimum method for administration of biosynthetic human growth hormone: a randomised crossover trial of an Auto Injector and a pen injection system

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Accepted 27 March 1992

Abstract

The use of optimum conventional growth hormone administration, using a growth hormone vial combined with an Auto Injector, was compared with a pen injection system using a cartridge of growth hormone. In both methods of administration the concentration of growth hormone was 16 IU/ml. Thirty patients (22 boys, eight girls) who had all previously been treated with growth hormone (4 IU/ml) administered using needles and syringes (without an Auto Injector) were randomised into receiving one of either treatment for three months and then crossed over for a further three months. Fourteen patients (10 boys, four girls) initially received KabiVial 16 IU/ml combined with an Auto Injector while 16 patients (12 boys, four girls) were treated with KabiPen 16 IU/ml. Mean age in both groups was 9·6 years. The majority of patients in both groups were treated with a regimen of either 15 or 20 units/m^2/week as a daily subcutaneous injection. Of the 30 patients who started in this trial, two who commenced using an Auto Injector refused to change to a pen system and were excluded from further analysis. When scored on a scale of -5 to $+5$ general convenience when changing from an Auto Injector to the KabiPen decreased from $+4·7$ to $+1·0$. When assessed for pain, the Auto Injector group scored $+4·7$, which decreased to $-0·2$ (more painful) for the pen. At the end of the trial 23 patients (82%) chose to continue with the KabiVial/Auto Injector combination as they found this less painful and the child did not see the needle or need to insert the needle manually. Five patients (18%) continued with the KabiPen as they considered the device smaller and easier to use. The accuracy of dosing using KabiVial was 100% compared with the range of 88% to 111% using KabiPen as the latter was available only in 0·5 unit increments. No growth hormone was wasted using KabiVial, although a mean of 0·6 units was wasted with every 16 IU cartridge in the KabiPen system.

It is concluded that patients should be able to contribute to the choice of growth hormone delivery systems and that newer methods need careful assessment.

(*Arch Dis Child* 1992;67:994–997)

Biosynthetic human growth hormone has traditionally been administered using a powdered growth hormone preparation in a vial to which diluent is added before the resulting solution is drawn up into a smaller syringe before injection. This is a relatively inconvenient form of preparation. Kabi Pharmacia have developed a new range of convenience products which are superior in that the growth hormone powder and water are present in the same applicator and are mixed by closing a syringe barrel (fig 1). Administration is by either needles and syringes or as a cartridge in a pen injection system.[1] Both of these new formulations of biosynthetic human growth hormone (Genotropin) are prepared in an identical concentration of 16 IU/ml.

Previous trials of a pen injection system against conventional application by needles and syringes have been biased because the volume of injection has been unequal when comparing the two systems,[1–3] which may be of particular significance when assessing pain. Although a pen injection system may offer a significant improvement in convenience, the patient still has manually to insert the needle subcutaneously. However, pen injection systems have not been evaluated against optimum treatment using an Auto Injector (which uses a 1 ml syringe and needle), a spring loaded device which automatically inserts the needle subcutaneously and delivers the injection.

The dose of growth hormone administered should be related to the patient's size.[4] Concern has previously been expressed about the dose regimen using a KabiPen injection system as only 0·5 unit increments are available up to a maximum of only 4·0 units, which severely limits its use in very small children and adolescents respectively, as well as reducing the dosage accuracy.[5]

We have used KabiVial (16 IU/ml) in combination with an Auto Injector and compared this device to a KabiPen (16 IU/ml) in order to determine which method was preferred by the patients and their parents. In addition we have examined the accuracy of dose administration and the potential wastage of growth hormone between the two systems.

Patients and methods

Thirty patients were randomly selected from the Growth Clinic at the Hospital for Sick Children, Great Ormond Street, all of whom were being treated with biosynthetic human growth hormone (Genotropin 12 IU, Kabi Pharmacia) which is a vial of growth hormone reconstituted in a solution of 4 IU/ml. The majority of patients had isolated idiopathic growth hormone deficiency (n=18); the other diagnostic groups were idiopathic multiple

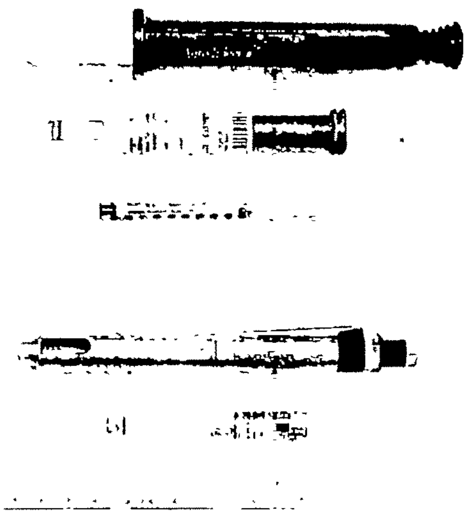

Figure 1 At the top of the figure is an Auto Injector and 1 ml syringe and needle with a KabiVial 16 IU/ml At the bottom of the figure is KabiPen with a KabiPen 16 IU/ml cartridge. A scale in cm is indicated

pituitary hormone deficiency (n=3), hypopituitarism after cranial irradiation (n=4), and dysmorphic syndromes (n=5). One of the latter children had Ehler-Danlos syndrome with easy bruising as part of his symptoms. Growth hormone in all the patients was administered by needles and syringes and none had previously used a pen injection system or an Auto Injector. All patients were selected by receiving a dose regimen of under 4 IU per day (the maximum dose which can be administered by KabiPen). After obtaining parental consent to participate in this study, patients were randomised to either three months of growth hormone administered by a pen injection system (KabiPen) or using KabiVial in combination with an Auto Injector (Owen Mumford Ltd). Mean age in the two groups was 9·7 years (range 3·3–13·7) in one group and 9·6 years (range 5·1–16·6) in the other. Sex distribution was similar in the two groups: 14 patients (10 boys, four girls) and 16 patients (12 boys, four girls) respectively. Surface area was similar in both groups: 1·0 m^2 (range 0·5–1·8) and 0·95 m^2 (range 0·6–1·5).

After a three month period all patients completed a questionnaire and then changed to a further three months of treatment with the alternative method of administration and completed a further questionnaire. These were completed in the presence of a growth research nurse (GH) and both pain of injection and general convenience were rated on a scale of −5 to +5. At the end of the six month period the children were allowed to continue with whichever treatment method they preferred.

Growth hormone administration was calculated as a weekly total dose related to surface area and divided equally into seven daily subcutaneous injections. The dose regimen of growth hormone administration was similar in both groups: the majority received either 15 IU/m^2/week (n=4 in both groups) or 20 IU/m^2/week (n=7 in both groups). A few patients received higher dose regimens of 25 or 30 IU/m^2/week but were similarly distributed in both treatment groups. The daily dose of growth hormone was calculated and allocated to the closest 0·5 unit increment available when using the pen system, and the difference in dose allocation between KabiVial and KabiPen was calculated as a percentage. Growth hormone remaining in the cartridge of the KabiPen, after the last full daily dose was administered, was calculated. As these products are designed for patient convenience, only one injection was permitted for each day.

Ethical committee approval was obtained for this study. Statistical analysis was by paired *t* test.

Results

Thirty patients started in this study, but after the first three months two patients refused to change from KabiVial/Auto Injector. Both children found the main advantage of an Auto Injector was that they did not have to insert the needle manually. These two patients were excluded from the rest of the analysis. At the end of the study 23 patients (82%) wished to continue with KabiVial/Auto Injector. The predominant reasons given were that this was less painful (n=16), the needle was not seen (n=4), and the needle was not inserted manually (n=3). Five patients (18%) elected to continue with the KabiPen. This was considered easier to use, especially as it was smaller (n=3), more 'gentle' (n=1, this was the child with Ehler-Danlos syndrome who had easy bruising), and less painful (n=1). This result was similar irrespective of which group the patients were initially randomised to. Of those continuing with KabiVial/Auto Injector after the trial had finished, nine patients (75%) were from the group who initially received an Auto Injector, whereas 13 patients (81%) initially received the KabiPen.

Ten children (36%) initially gave their own injections before this trial commenced, and these were equally distributed between the two groups. After the six months of this trial, 16 children (57%) gave their own injections; 12 out of 23 (52%) of those continuing with a KabiVial/Auto Injector and four out of five (80%) of those continuing on the KabiPen injector system. The results of the patients' scoring of the different methods of growth hormone application are given in fig 2. When scored for general convenience, changing from the Auto Injector to the KabiPen, the score decreased from +4·7 to +1·0 ($p<0·001$) and when scored for pain the decrease was from +4·0 to −0·2 ($p<0·001$).

The accuracy of dosage administration was 100% using KabiVial whereas the range of dose variation was between 88% and 111% using KabiPen, which relates to the fixed 0·5 unit increments between dose schedules. No wastage of growth hormone occurred using KabiVial as at the end of the vial the remaining growth hormone was topped up using a new vial. However using the pen cartridge system the mean quantity of growth hormone remaining at the end of the cartridge was 0·6 units (range 0–1·0).

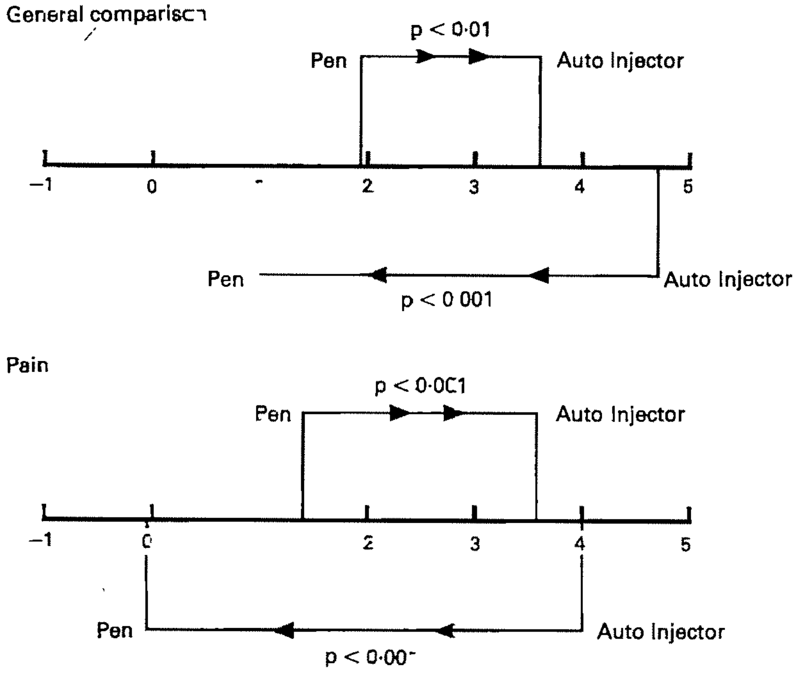

Figure 2 Graded patient scores (−5 to +5) after each three month period, with the baseline comparison made to the original method of growth hormone injection using needles and syringes.

Discussion

Our results suggest that the older method of growth hormone treatment using a syringe but combined with an Auto Injector is superior to a pen injection system both when assessed by the patients for convenience and pain as well as for dosage considerations. The predominant advantage for compliance was due to the Auto Injector's ability both to insert the needle and administer the injection rapidly with the needle out of sight of the child and this advantage was greatly appreciated by the children. Certainly we would suggest that in children having difficulties with compliance it would be preferable to use an Auto Injector rather than a pen injection system. However a few children did prefer the KabiPen (five out of 28) mainly because the device was small and there was no noise associated with its use. The patients' scoring indicated that the KabiPen may be more acceptable if it is used as the initial method of growth hormone administration. It is interesting that the majority of children continuing with the pen injector system gave their own injections whereas only 50% of those continuing with an Auto Injector self administered. Earlier studies have suggested that a pen injection system was superior to using needles and syringes.[1-3] These have not combined treatment using an Auto Injector to optimise conventional treatment and have compared applicators using different concentrations of growth hormone. It is unfortunate that although the KabiPen injection system is supplied free of charge to the patients, the same does not apply to an Auto Injector. All the patients found the technique of obtaining growth hormone in solution considerably simpler and more convenient using both KabiVial and KabiPen than older growth hormone multidose vials.

All the patients involved in this study were taught by an experienced growth research nurse. Certainly this may well account for the increased number of children administering their own injections during the study. Unfortunately, from the nature of the applicators involved, it was not possible to make this a double blind study. Our study was designed to take into account the limitations of the maximum dose of KabiPen of 4 units per day, which severely restricts the use of this device in pharmacological regimens of growth hormone treatment, especially high dose growth hormone regimens used in girls with Turner's syndrome.[5] In addition this accounted for why we had a younger mean age group of patients than would have been otherwise expected, which may bias the study further. For reasons of convenience, growth hormone treatment was only injected once daily and this led to a residue of growth hormone in the KabiPen cartridge whereas there was no corresponding waste using a vial. Of course, there is the possibility of using different dosages of growth hormone on different days of the week in order to avoid wastage but this would imply a complicated regimen that may be counterproductive in terms of compliance.

Certainly the most important decision of which applicator to use, in terms of convenience, should be made by the child/parent. Although growth hormone from a vial combined with an Auto Injector may be more complicated to prepare, the simplicity and passivity of the injection technique outweighs the advantages of a pen injector system. Additionally, in terms of dosage consideration, a vial is more accurate and less wasteful of expensive resources. Of course the KabiPen injection system would be improved if doses greater than 4 units could be administered and if dose increments were acceptable in less than 0·5 units. It is unlikely that more than one growth hormone injection per day[6] is necessary to optimise growth response and so the convenience of a relatively portable pen device becomes minimal, in contrast to the experience of an insulin pen injection system in the treatment of diabetes mellitus. Great care should be taken in advising patients about injection techniques and we recommend that children/parents are shown the alternative methods available and then they are able to make their own choice. This may well be of great significance for compliance to growth hormone treatment, which is probably far worse than had previously been appreciated (S L Smith, C G D Brook. Paper presented to the British Society for Paediatric Endocrinology, November 1991). The KabiPen injector combined with an Auto Injector function would probably be the optimum device for delivering growth hormone. However, whichever method is used, we believe that the involvement of a nurse specialist, time taken to explain treatment options, teaching and follow up, remain an essential element of the therapeutic regimen.

G Hamill was funded by the Child Growth Foundation L Moyle was supported by Kabi Pharmacia (UK) We are grateful to Serono (UK) for financial assistance in the preparation of the manuscript

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Cutting the corpus callosum for intractable epilepsy

There can be few clinical problems more distressing for families and doctors then truly intractable epilepsy. The medical approach to the problem has been admirably summarised by Aicardi.[1] What about surgery?[2] Few of these patients are suitable for conventional resective surgery but there is increasing interest in the use of anterior callostomy. A recent report from Montreal (Hirokazu Oguni and colleagues, *Annals of Neurology* 1991;**30**:357–64) describes the results of this operation in 43 patients followed up for at least a year. The youngest was 7 years old and the oldest 60 but, unfortunately, detailed information about the ages of the patients is not given. Nevertheless, from the types of epilepsy being treated it is reasonable to assume that many were children. (It would be very helpful if research workers presenting data on a mixed population of children and adults would give specific information about the children. A recent report on the withdrawal of antiepileptic treatment[3] was almost impossible to analyse from the paediatric point of view because of the lack of such information.)

There was no operative mortality in this series but postoperative complications of varying severity occurred in 16 of the 43 patients. None gave rise to permanent morbidity and no clinically significant longlasting neurological disturbance resulted from the surgery. The results were better with more extensive surgery and it is now the policy in Montreal to divide the anterior two thirds of the corpus callosum.

The results are encouraging, the effect on seizure control being 'good' in 33% and 'worthwhile' in 56%. It might be expected that callostomy would benefit most those with seizures of focal origin with secondary generalisation and there was some evidence in this series that this was so but significant benefit was also seen in apparently primarily generalised epilepsy. Only six of the 43 patients were of normal intelligence and many were severely retarded. Improvement after operation occurred at all levels of intelligence. Small increases in measured IQ were found in those whose epilepsy improved. Of particular interest to paediatricians is the finding that eight of 14 patients with the Lennox-Gastaut syndrome gained significant benefit from the operation.

The apparent success of this operation poses considerable logistic problems. Neurosurgeons with a specific interest in epilepsy surgery are few, as are centres with the appropriate staffing and facilities for assessment of these patients but patients who might be considered for surgery are many. The implications for the organisation of services for children with epilepsy are potentially very great.

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Archives of Disease in Childhood 1992; 67: 998–1002

Plasma and cerebrospinal fluid arginine vasopressin in patients with and without fever

P M Sharples, J R Seckl, D Human, S L Lightman, D B Dunger

Abstract

Hyponatraemia has been described in association with a number of acute infectious diseases, mainly bacterial and tuberculous meningitis and pneumonia, and has been attributed to inappropriate secretion of arginine vasopressin (AVP). The mechanism of inappropriate AVP production is uncertain, but there is experimental evidence to suggest that fever may stimulate secretion of AVP into plasma and cerebrospinal fluid. In this study, AVP concentrations in plasma and cerebrospinal fluid from 37 febrile children with infections have been compared with those from 27 afebrile control subjects. Ten of the febrile children had meningitis (eight bacterial, two viral) and the remainder a variety of other infectious diseases. Seventy four per cent of febrile infected children were hyponatraemic (serum sodium <135 mmol/l) compared with only 8% of the afebrile controls. Plasma AVP concentrations were significantly higher in the febrile patients (median 2·92 pmol/l, range 1·0–23·25, n=28) than in controls (median 1·67 pmol/l, range 0·57–6·0, n=14) but there was no significant difference in cerebrospinal fluid AVP concentrations. There was no difference in plasma AVP concentrations between patients with meningitis and those with infections not involving the central nervous system. Careful attention should be paid to fluid and electrolyte balance in all children with acute infections.

(*Arch Dis Child* 1992;67:998–1002)

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Accepted 10 April 1992

Hyponatraemia and water retention have been reported in children with bacterial and tuberculous meningitis,[1–4] viral encephalitis[5] and pneumonia.[4 6 7] These findings have been attributed to inappropriate secretion of arginine vasopressin (AVP) and in a few studies plasma or cerebrospinal fluid AVP concentrations have been measured and shown to be increased.[1 6 8] The mechanism of the inappropriate AVP production in these situations remains uncertain,[8] although it has been suggested that increased AVP concentrations in pneumonia may be the result of intrathoracic pathology interfering with the normal modulation of AVP release via stretch and baroreceptors in the left atrium and carotid sinus.[9]

Experimental studies have indicated that in a variety of animal species, AVP production, hyponatraemia and hypo-osmolality can be produced by inducing pyrexia.[10–12] These observations have led to suggestions that AVP may have a role as an endogenous antipyretic.[13 14] This hypothesis might explain the findings of Gonzalez *et al* who noted an association between hyponatraemia and a variety of acute infections.[15] However, there is little published information concerning plasma or cerebrospinal fluid AVP concentrations in acute infections other than those of the central nervous or respiratory systems.

The aim of this study was to determine the concentrations of AVP in samples of plasma and cerebrospinal fluid obtained from febrile children with a variety of infectious diseases and compare these with the concentrations found in a group of afebrile control children.

Patients and methods

The study population comprised 37 febrile children with a variety of acute infectious illnesses (table 1). Ten children had meningitis (eight bacterial, two viral). The median age of the study population was 2·5 years, range 2 weeks–14 years; 20 (54%) were boys. All the children were hospital inpatients. Samples were obtained shortly after admission at a time when venepuncture or lumbar puncture was being performed for a clinical indication. The body temperature was recorded immediately before

Table 1 Details of the febrile children

Patient No	*Age (years)*	*Sex*	*Diagnosis*
1	10	F	Pneumonia
2	2·5	F	Upper respiratory tract infection
3	1·5	M	Salmonella enteritis
4	11	M	Pyrexia of unknown origin
5	1·33	M	Viral illness
6	12	M	Urinary tract infection
7	14	F	Urinary tract infection
8	5	M	Viral illness
9	0·75	M	Viral illness
10	1·66	F	Viral illness
11	1·33	F	Tonsillitis
12	1·0	F	Cellulitis
13	3	F	Viral illness
14	9	M	Otitis media
15	1	F	Otitis media
16	1	M	Viral illness
17	0·16	M	Pneumonia
18	0·16	M	Viral illness
19	11	M	Upper respiratory tract infection
20	10	M	Osteomyelitis
21	0·50	F	Otitis media
22	5	F	Viral illness
23	1·5	F	Upper respiratory tract infection
24	0·04	F	Viral illness
25	1·75	M	Cellulitis
26	5	M	Viral illness
27	13	M	Viral illness
28	2·5	F	Bacterial meningitis
29	12	F	Bacterial meningitis
30	7	M	Bacterial meningitis
31	9	F	Bacterial meningitis
32	0·25	M	Bacterial meningitis
33	8	F	Bacterial meningitis
34	1·42	F	Bacterial meningitis
35	1	M	Bacterial meningitis
36	5	M	Viral meningitis
37	7	M	Viral meningitis

sampling. Plasma samples for AVP determination were obtained from 28 febrile children and cerebrospinal fluid samples from 19. Paired plasma and cerebrospinal fluid samples were obtained in nine of the children. No child was hypotensive or clinically dehydrated at the time of sampling.

The afebrile control population consisted of two groups, totalling 27 children: 15 children who were seen as outpatients for a variety of conditions (table 2), and from whom plasma samples were obtained, and 12 inpatients who underwent lumbar puncture for various clinical indications (table 3) and who provided cerebrospinal fluid samples. The median age of the control population was 7·0 years, range 1 month–15 years; 13 (48%) were boys. There was no significant difference between the age structure of the study and control groups (Mann–Whitney U test, p=0·13).

Blood (0·5–1·0 ml) was taken onto ice, centrifuged immediately, and the plasma separated and stored at −20°C until assay. Cerebrospinal fluid (0·5 ml) was also taken onto ice and stored at −20°C. Immediately before AVP assay, the plasma sample was extracted through octadecasilyl silica cartridges (Sep-pak C18, Waters Associates). The AVP concentration in plasma and cerebrospinal fluid was measured by radioimmunoassay, as described previously.[16] The intra-assay coefficient of variation was 5% and the interassay coefficient of variation 15%. The limit of detection of the assay was 0·30 pmol/l. In the data analysis, a non-detectable concentration of AVP was assigned a value of 0·00 pmol/l.[8]

The study was approved by the local ethical committee.

Table 2 Details of the afebrile children who provided plasma samples

Patient No	*Age (years)*	*Sex*	*Diagnosis*
1	4	M	Asthma
2	0·25	F	Skeletal dysplasia
3	0·83	M	Constipation
4	0·04	M	Feeding difficulties
5	10	F	Bell's palsy
6	5	F	Asthma
7	2	M	Failure to thrive
8	1	M	?Breath holding attacks ?Fits
9	8	F	Acute leukaemia
10	14	M	Constitutional short stature
11	12	F	Friedreich's ataxia
12	13	M	Constitutional short stature
13	0·75	F	Failure to thrive
14	15	M	Constitutional short stature
15	12	F	Diabetes mellitus

Table 3 Details of the afebrile children who provided cerebrospinal fluid samples

Patient No	*Age (years)*	*Sex*	*Diagnosis*
1	0·02	F	?Seizure
2	0·58	M	Seizures
3	14	M	Headache ?meningitis
4	13	F	Staging for acute leukaemia
5	10	F	Staging for acute leukaemia
6	11	M	Neck stiffness ?meningitis
7	11	M	Guillain–Barré syndrome
8	5	M	Epilepsy
9	9	F	Headache ?meningitis
10	4	F	Staging for acute leukaemia
11	7	F	Staging for non-Hodgkin's lymphoma
12	15	F	Staging for acute leukaemia

Results

Figure 1 shows the plasma AVP results obtained in febrile and afebrile patients. The plasma AVP concentrations obtained from the febrile children (median 2·92 pmol/l, range 1·00–23·25) were significantly higher than those obtained from the afebrile controls (median 1·67 pmol/l, 0·57–6·0) (Mann-Whitney U test, p=0·003). The difference between febrile and afebrile subjects persisted if children with meningitis were excluded from the analysis (median plasma AVP concentration among febrile, non-meningitic patients 2·49 pmol/l, range 1·0–23·25) (Mann-Whitney U test, p=0·036). Plasma AVP concentrations in the meningitic children (median 4·14 pmol/l, range 1·16–15·25, n=6) were not in fact significantly different from those observed in the other febrile children (Mann–Whitney U test, p=0·10). There was no difference in plasma AVP concentrations according to sex, either when all the patients were considered together (Mann-Whitney U test, p=0·10) or in the febrile and afebrile subgroups. There was also no correlation between plasma AVP concentration and age (r= −0·06, p=0·70).

There was no significant difference between the cerebrospinal fluid AVP concentrations obtained from the febrile study children (median

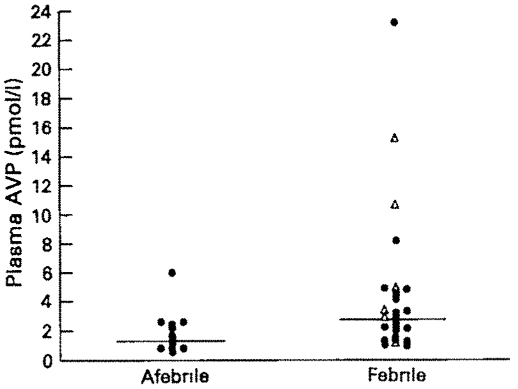

Figure 1 Plasma AVP concentrations (pmol/l) in febrile children with acute infections compared with febrile control children. Among the febrile children, the triangular symbols represent those with bacterial or viral meningitis and the circular symbols, those with other acute infections.

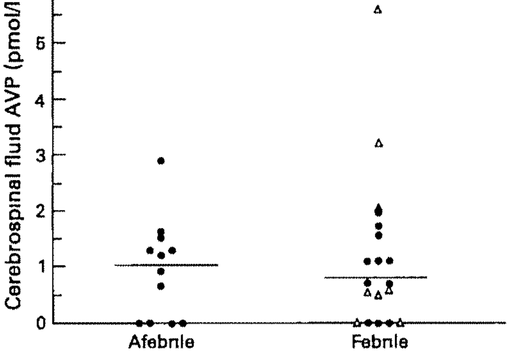

Figure 2 Cerebrospinal fluid AVP concentrations (pmol/l) in febrile children with acute infections compared with afebrile control children. Among the febrile children, the triangular symbols represent those with bacterial or viral meningitis and the circular symbols, those with other acute infections.

0·7 pmol/l, range 0–5·57) and those obtained from the afebrile control children (median 1·06 pmol/l, range 0–2·9) (Mann–Whitney U test, p=0·38) (fig 2). There was also no significant difference between the AVP cerebrospinal fluid concentrations obtained from children with meningitis (median 0·56 pmol/l, range 0–5·57, n=8) and those obtained from other febrile children (median 0·90 pmol/l, range 0–1·98, n=10) (Mann–Whitney U test, p>0·05). As with the plasma results, no correlation was found between cerebrospinal fluid AVP concentration and age (r=0·22, p=0·10) and there was also no significant difference in the results obtained from boys and girls (Mann–Whitney U test, p=0·24).

Figure 3 illustrates the relationship between body temperature and plasma AVP concentrations in the febrile children. There was no correlation between body temperature and plasma AVP concentration (r=0·09), p>0·05). There was also no correlation between body temperature and cerebrospinal fluid AVP concentration (fig 4) (r=0·23, p>0·05). Among the nine children from whom paired plasma and cerebrospinal fluid samples were obtained, there was no significant correlation between plasma and cerebrospinal fluid AVP concentrations (r=0·32, p=0·40).

Serum sodium concentrations, obtained concomitantly, were available for 23/37 (62%) febrile study patients and 12/27 (44%) afebrile control children. The serum sodium concentrations observed in febrile children (median 132 mmol/l, range 129–140) were significantly lower than those in the 12 afebrile study children (median 138 mmol/l, range 133–143) (Mann–Whitney U test, p=0·002). There were 17/23 (74%) febrile children who were hyponatraemic (serum sodium concentration less than 135 mmol/l),[4] whereas only one afebrile control child was hyponatraemic. Six (35%) of the hyponatraemic febrile children had meningitis but the remaining 11 had other acute infections. There was no significant difference between the serum sodium results obtained from the children with meningitis (median 132 mmol/l, range 131–139, n=7) and those obtained from the other febrile children (median 133 mmol/l, range 129–140, n=16) (Mann–Whitney U test, p=0·33). There was no correlation between serum sodium concentration and plasma AVP concentration in the febrile children (r=0·04, p>0·50) nor between serum sodium and cerebrospinal fluid AVP concentration (r=0·46, p=0·18).

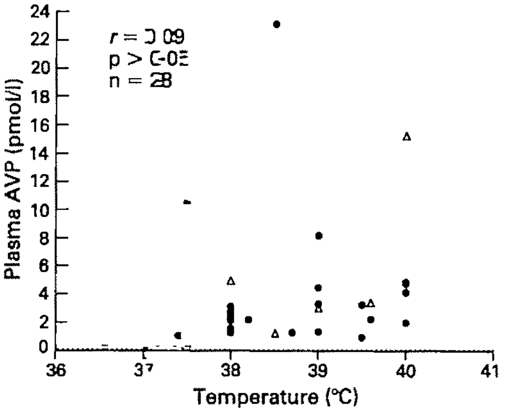

Figure 3 Relationship between body temperature and plasma AVP concentration (pmol/l) for the 28 febrile children from whom plasma samples were obtained. The triangular symbols represent children with bacterial or viral meningitis and the circular symbols represent children with other acute infections.

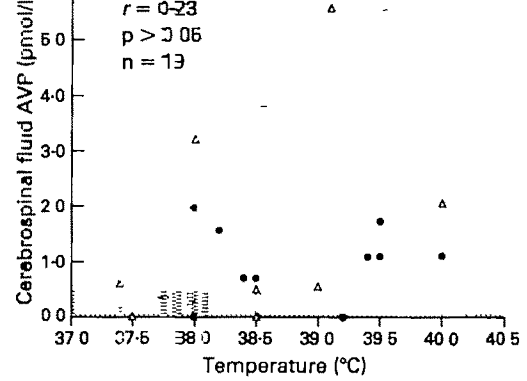

Figure 4 Relationship between body temperature and cerebrospinal fluid AVP concentration (pmol/l) for the 19 febrile children from whom cerebrospinal fluid samples were obtained. The triangular symbols represent children with bacterial or viral meningitis and the circular symbols represent children with other acute infections. The shaded area indicates the lower limit of detection of the assay.

Discussion

The results of this study demonstrate that increased plasma concentrations of AVP occur not only in children with bacterial meninigitis, viral encephalitis and pneumonia, as previously reported, but also in association with a wide range of other acute infections. The occurrence of detectable plasma concentrations of AVP in children with low serum sodium results (<135 mmol/l) confirms the inappropriate nature of the AVP secretion. Hyponatraemia has been previously described in acutely febrile children,[15] and there have been a number of isolated case reports reporting inappropriate AVP secretion in tetanus,[17] viral meningitis,[18] and Rocky Mountain spotted fever.[19] However, no previous study has demonstrated increased AVP production in such a variety of acute infections.

None of the children in this study were on treatment recognised to be associated with increased AVP production, such as vincristine, chlorpropramide, tricyclic antidepressants, or phenothiazines.[9] Increased AVP production may occur in response to pain or anxiety,[9 20 21] and increased concentrations in unanaesthetised children might in part reflect the stress associated with venepuncture or lumbar puncture in this age group. However, there seems no reason to suppose that this effect would be confined to the study children, particularly as the age structure of the study and control groups was similar.

In this study, there was a significant difference between plasma AVP concentrations from febrile and afebrile patients, but no significant difference in the cerebrospinal fluid AVP concentrations between study and control groups. It is possible that this may reflect the difficulty of establishing 'control' cerebrospinal fluid values in a paediatric population. There were 5/12 (42%) afebrile control children who underwent lumbar puncture because of an actual or suspected abnormality of the central nervous system (table 3) and increased cerebrospinal fluid AVP concentrations have been described in association with a variety of non-infectious central nervous system pathologies.[16 22–25] Another methodological consideration is the fact that it was not possible to standardise the time of day at which the samples were obtained; discrepancies in the sampling times might therefore have obscured differences between groups in the cerebrospinal fluid AVP concentrations.[26] However, no diurnal rhythm of AVP cerebrospinal fluid concentration has been demonstrated in humans.[27] Moreover, it is recognised that under physiological conditions, AVP concentrations in cerebrospinal fluid and blood are differentially regulated[26] and that various stimuli which increase plasma AVP concentrations may produce little alteration in cerebrospinal fluid levels.[28] Even when stimulatory effects are found, AVP release into cerebrospinal fluid has a greater threshold than release into blood.[26] In the nine cases in this study, in whom paired blood and cerebrospinal fluid samples were available, there was no correlation between plasma and cerebrospinal fluid AVP concentrations. Indeed, it has been suggested that the increased AVP concentrations in cerebrospinal fluid described in meningitic children are the result of leakage from the circulation across a damaged blood–brain barrier, rather than the result of increased intracerebral production,[8] and this hypothesis would be in keeping with our observations.

The results of this study do not give any indication of the pathogenetic mechanism responsible for the increased plasma concentrations of AVP. The lack of correlation between body temperature and plasma and cerebrospinal fluid AVP concentrations is in contrast to the results of some experimental studies, in which a relationship between pyrexia and AVP production has been demonstrated,[12 14] but in agreement with the results of others, in which a direct correlation was not found.[10 12] It may be that, in some species, fever has an 'all or nothing' effect on AVP production or that a single temperature measurement does not reflect accurately the degree of stimulus to AVP secretion. Alternatively, the mechanism of the increased AVP production in children with acute infections may be unrelated to the occurrence of fever; certainly, there is experimental evidence to suggest that the role of AVP as an antipyretic may vary between species.[29 30] Increased plasma concentrations of AVP have been described in burned children[31] and in postoperative paediatric surgical patients,[32] and it has been suggested that the increased concentrations probably represent part of the body's stress response.[9 32] Increased AVP production in acute infections may occur for the same reason.[33]

The finding that inappropriate AVP production and hyponatraemia is not an uncommon phenomenon in febrile children with a variety of acute infections indicates that the serum sodium concentration should always be determined before administering intravenous fluid in such patients. The significance of the inappropriate AVP production, in terms of implications for outcome, is uncertain and was not explored in this study. Among children with bacterial meningitis, both the degree of hyponatraemia on admission and its duration seem to correlate with long term outcome[34] and this has been attributed to the effect of AVP on brain water permeability and cerebral oedema.[35] Although this may seem at first to have little relevance to children with infections not involving the central nervous system, it has been suggested that AVP has a role in the pathogenesis of febrile convulsions through its effect on brain water permeability.[36] In this study, eight children (median age 1·6 years, range 1·0–5) underwent lumbar puncture after a presumed febrile convulsion; there was no significant difference in the plasma or cerebrospinal fluid AVP concentrations obtained from these children and those obtained from febrile children in the age group at risk from febrile convulsions (6 months–6 years[37]) who did not have convulsions (Mann–Whitney U test: p=0·10 for plasma; p=0·08 for cerebrospinal fluid). However, in view of the small numbers, further studies would be necessary to explore this issue and to investigate the relationship between AVP production and hyponatraemia and eventual outcome in febrile infected children.

We would like to acknowledge all the medical and nursing staff at the John Radcliffe Hospital who assisted with the sample collection and Drs J Kay, A Foot, and P Holland for their help. JRS is a Wellcome Senior Fellow in Clinical Science.

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Maternal chickenpox

Maternal chickenpox in early pregnancy has been associated with abnormalities in the fetus including microphthalmia, cataracts, Horner's syndrome, microcephaly, and growth defects of limbs, fingers, and muscles. Congenital varicella syndrome was found in three of 61 patients (5%) in three previously reported studies. Now another 40 mothers with first trimester chickenpox have been reported from Connecticut (James Balducci and colleagues, *Obstetrics and Gynecology* 1992;**79**:5–6). One mother elected for termination of pregnancy and three had spontaneous abortions. There is no comment about abnormality in these fetuses. One fetus was shown by ultrasound examination to have a large omphalocele and the pregnancy was terminated. None of the pregnancies was complicated by congenital varicella syndrome as previously described.

Maternal chickenpox is not common because most mothers have had the disease in childhood. These authors quote an incidence of 0·7 per thousand pregnancies but it is not clear whether that figure is for chickenpox at any stage in pregnancy or just the first trimester. In any event congenital varicella syndrome is rare but it should disappear altogether with chickenpox immunisation (see Archivist 1991:1212).

ARCHIVIST

Archives of Disease in Childhood 1992, 67: 1003–1007

Cord blood lymphocyte responses to food antigens for the prediction of allergic disorders

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Accepted 18 February 1992

Abstract

Proliferative responses of cord blood lymphocytes (CBLs) to food antigens and cord blood IgE concentrations were measured in 37 full term newborn infants for the prediction of allergic disorders. In these 37 infants who were followed up for two years, allergic history of the family was found in four (sensitivity 57·1%) and cord blood IgE concentrations were greater than 0·5 IU/ml in three (sensitivity 42·9%) of seven infants who developed allergic disorders. When CBLs were stimulated twice by ovalbumin or bovine serum albumin, the value of the stimulation index in proliferative responses of CBLs to ovalbumin or bovine serum albumin was greater than 1·5 in six (sensitivity 85·7%) of seven infants who developed allergic disorders. The specificity of the responses of CBLs in the prediction of the development of allergic disorders was 93·3%. The proliferative responses of CBLs to food antigens were useful in the prediction of not only development of allergic disorders but also offending allergens. These observations provide further evidence that sensitisation is occurring in utero. This would appear to be increasingly important in the genesis of early atopic problems. As our follow up is only two years, in utero sensitisation is a prediction for the early development of atopic disease but only longer follow up will show whether this holds good for allergic disorders at any age.

(*Arch Dis Child* 1992,67:1003–1007)

Allergy often begins early in life,[1 2] in many cases during the first year. Patients who suffer from allergic diseases are very difficult to cure completely. Prevention of allergic disorders in infants has been attempted by means of food and aeroallergen avoidance.[3] The detection of a newborn at high risk of allergy is therefore important. Michel *et al*,[4] and Magnusson[5] reported that the IgE concentrations of cord blood appeared to be a good predictor of the development of allergy during infancy. However, it is not sufficient to predict 'high allergic risk newborns' on the basis of increased IgE concentrations of cord blood alone, because a raised cord blood IgE concentration is specific but not sensitive in the prediction of the development of allergic disorders.[5–7] Moreover, Ruiz *et al* report that maternal blood may have contaminated cord blood in 7% of their cases.[8] Allergic disorders that begin early in life are often atopic dermatitis and food allergy such as hens' egg and cows' milk sensitivities. We previously reported that the combination of the radioallergosorbent test and the detection of proliferative responses of peripheral blood lymphocytes to each food allergen is very useful in the diagnosis of hypersensitivity in children with atopic dermatitis who are sensitive to each food.[9] In this study, cord blood IgE concentrations and proliferative responses of cord blood lymphocytes (CBLs) to each food antigen were measured for the prediction of the development of allergy during infancy.

Subjects and methods

SUBJECTS

Thirty seven full term newborn infants were investigated. Cord blood was collected immediately after birth by direct needle aspiration of the umbilical vein.

CORD BLOOD IgE CONCENTRATIONS

Cord blood IgE concentrations were measured by the enzyme linked immunoassay as previously described by Pene *et al* using a rabbit anti-IgE immunoglobulin (Dako), a murine antihuman IgE monoclonal antibody (Medical Biological Laboratory), and a goat antimouse immunoglobulin coupled to alkaline phosphatase (Sigma).[10] A standard IgE serum (Behring) was used as a reference. The limit of the sensitivity of the assay was 0·1 IU/ml.

CELL PREPARATION AND CULTURE

CBLs were isolated from heparinised cord blood by gradient centrifugation in Ficoll-Paque (Pharmacia). CBLs were suspended to give a density of 10^6/ml in the culture medium consisting of Roswell Park Memorial Institute 1640 medium supplemented with 15% pooled human AB$^+$ serum, L-glutamine (2 mM), penicillin (100 units/ml), and streptomycin (100 µg/ml). In the case where CBLs were stimulated once by each food antigen, CBLs (2×10^5) were cultured at 0·2 ml per well in round bottomed microtest plates (A/S Nunc) with or without various concentrations of food antigens (0·25, 2·5, 25 µg/ml, respectively) at 37°C for four days in a humidified atmosphere containing 5% carbon dioxide.[9] In the case where CBLs were stimulated twice by each food antigen, CBLs (10^6/ml) were preincubated at 2 ml per tube in the culture test tube with or without each food antigen (2·5 µg/ml) at 37°C for various numbers of days in a humidified atmosphere containing 5% carbon dioxide. Thereafter, cells were washed three times with phosphate buffered saline and resuspended to give a density of 10^6/ml in the culture medium. Subsequently, the CBLs (2×10^5) were cultured at 0·2 ml per well in round bottomed microtest plates with or without various concentrations of the same food antigen (0·25, 2·5, 25 µg/ml, respectively) at 37°C for various numbers of days in a humidified atmosphere containing 5% carbon dioxide.

PROLIFERATIVE RESPONSES

DNA synthesis was measured by adding 0·5 µCi [^{3}H] thymidine (specific activity: 43 Ci/mmol, Amersham) per well four hours before harvesting onto glass fibre filters. ^{3}H incorporation was measured by liquid scintillation counting, and the results were expressed as the mean of a triplicate. To compare responses between individuals, we also expressed the results as a stimulation index (SI; cpm, counts/minute).

$$SI=\frac{\text{Mean cpm in cultures stimulated with food antigens}}{\text{Mean cpm in unstimulated cultures}}$$

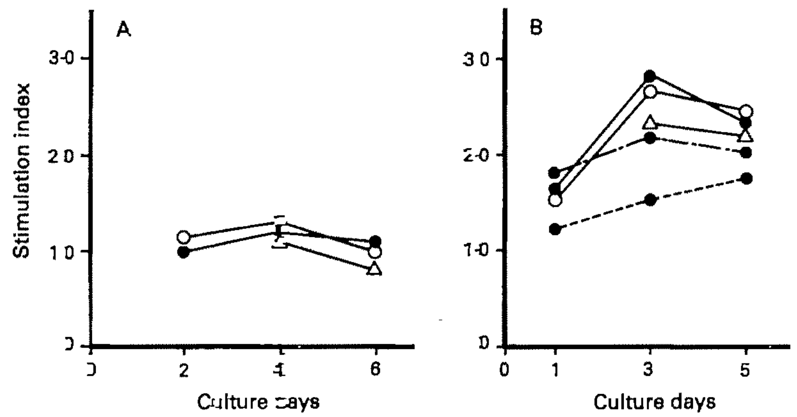
ANTIGENS

Ovalbumin and bovine serum albumin were purchased from Wako Junyaku (Japan). The purity of ovalbumin or bovine serum albumin used was confirmed by sodium dodecylsulfate polyacrylamide gel electrophoresis as a single band, 45 K or 66 K, respectively.

CONDUCT OF THE STUDY

Cord blood IgE concentrations and proliferative responses of CBLs to each food antigen were measured at birth. The allergic history of the family (parents and siblings) was also investigated at that time.

All 37 newborn infants were followed up for two years. Allergic disorders or symptoms (atopic dermatitis, bronchial asthma, allergic rhinitis, food allergy, wheezy bronchitis) which developed in the infants were investigated. Clinical criteria that defined allergy were chosen according to those of Orgel *et al*,[1] and Kjellman.[11] Diagnosis of atopic dermatitis was defined by the criteria of Hanifin.[12] The severity of atopic dermatitis was graded by the food challenge symptom scores for skin of Bock *et al*.[13] Diagnosis of food allergy was defined on the basis of clinical history and double blind placebo controlled food challenges.[13] Consequently, the relationships among allergic history of the family (parents and siblings), cord blood IgE concentrations, proliferative responses of CBLs to each food antigen, and the development of allergic disorders in the infant for two years were investigated.



A time response study of proliferative responses of CBLs stimulated by ovalbumin. (A) Proliferative responses of CBLs stimulated once by ovalbumin. The X axis shows culture periods; ○——○: 25 µg/ml of ovalbumin, ●——●: 2·5 µg/ml of ovalbumin, △——△: 0·25 µg/ml of ovalbumin. (B) Proliferative responses of CBLs stimulated twice by ovalbumin. The X axis shows culture periods after three, five, or seven day preincubation with a concentration of 2·5 µg/ml of ovalbumin; ●——● cultures with 2·5 µg/ml of ovalbumin after three day preincubation, ○——○: cultures with 25 µg/ml of ovalbumin after five day preincubation, ●——●: cultures with 2 5 µg/ml of ovalbumin after five day preincubation, △——△. cultures with 0·25 µg/ml of ovalbumin after five day preincubation, ●— — ●. cultures with 2 5 µg/ml of ovalbumin after seven day preincubation

STATISTICAL ANALYSIS

Frequencies were compared by Fisher's exact test (2×2 contingency tables).

Results

PROLIFERATIVE RESPONSES OF CBLs TO EACH FOOD ANTIGEN

CBLs stimulated twice by ovalbumin or bovine serum albumin exhibited proliferative responses in some subjects. As the peak proliferation was seen under the culture conditions of five day preincubation and a subsequent three day culture with a concentration of 2·5 or 25 µg/ml of each antigen (figure), cultures were routinely harvested on these culture days. The maximal proliferative responses of CBLs stimulated once and twice by ovalbumin or bovine serum albumin for the whole series of all 37 subjects are shown in table 1, in the order of the values of the SI in responses to ovalbumin or bovine serum albumin. Although CBLs stimulated once by ovalbumin or bovine serum albumin showed no proliferative responses in any subject, CBLs stimulated twice exhibited proliferative responses in some subjects. For convenience, subjects were divided into two groups according to the values of the SI: greater than 1·5 and less than 1·5. SI values greater than 1·5 in either ovalbumin stimulation or bovine serum albumin stimulation were seen in eight (21·6%, subjects 1–8) of 37 subjects, as shown in table 1.

CORD BLOOD IgE CONCENTRATIONS AND ALLERGIC HISTORY OF THE FAMILY

Table 1 also shows cord blood IgE concentrations and the allergic history of the family for each subject. According to the report previously described by Michel *et al*,[4] subjects were divided into two groups according to the cord blood IgE concentrations: greater than 0·5 IU/ml and less than 0·5 IU/ml. Cord blood IgE concentrations were greater than 0·5 IU/ml in 10 (27·0%) of 37 subjects. There was allergic history of the family (parents and siblings) in 11 (29·7%) of 37 subjects.

RELATIONSHIP BETWEEN VARIABLES FOR PREDICTION

There was allergic history of the family (parents and siblings) in four (40·0%) of 10 subjects whose cord blood IgE concentrations were

Table 1 Cord blood IgE concentrations, proliferative responses of CBLs stimulated once or twice by ovalbumin or bovine serum albumin, allergic history of the family, and allergic disorders developed in infants who were followed up for two years

Subjects	*Allergic history of the family*	*Cord blood IgE (IU/ml)*	*Proliferative responses (SI**) of CBLs stimulated*				*Allergic disorders developed in infants*
			Once		*Twice*		*AD (severity, offending foods, onset) and WH (onset)*
			Ovalbumin	*Bovine serum albumin*	*Ovalbumin*	*Bovine serum albumin*	
1	B(AD)	1·1†	0 59	1 24	1·04	3·29†	AD (severe, cows' milk, 4 months)
2		0·2	1 23	1·51	2·81†	1 17	AD (moderate, hens' egg and soybean, 11 months)
3		<0 1	1·79	0 54	2·45†	2·15†	AD (mild, hens' egg, 8 months), WH (1 3 years)
4		2 3†	1·03	1·03	1·28	2 25†	
5	M(BA)	0 2	0 94	0·71	1 07	2 07†	AD (moderate, cows' milk, 4 months)
6	F(AR)	<0·1	0 78	0 95	1 82†	2 00†	AD (moderate, hens' egg, 1 year), WH (1 year)
7		2·7†	0 80	0 58	1·82†	1 27	AD (severe, hens' egg, 11 months)
8		0·7†	0·97	1 25	1·10	1·79†	
9	M(AR), B(AD)	0·3	0·72	0 69	1·44	1·16	
10		<0 1	0·97	0·77	0·99	1 34	
11	F(AR)	0·8†	0.92	0 84	0·94	1·31	
12		<0 1	0·66	1·01	1 27	0 83	
13		0 2	0·56	0·67	1 23	1 17	
14		<0·1	1·10	0·83	1 23	1 04	
15		<0·1	1 00	1·02	1 14	1 16	
16		<0·1	1·03	0·97	0 69	1 16	
17	F(AR)	0 3	0 73	0 84	0 97	1 14	
18		<0·1	0 77	0 70	0 92	1 11	
19		<0·1	1·26	1 25	0·95	1·09	
20		0·5†	0·71	1 15	0·69	1 01	
21	M(AD)	<0 1	1·03	0 73	0·90	0 97	
22		1 5†	0 61	0·43	0·67	0·94	
23		2 3†	0 98	0·79	0 88	0 90	
24	M(AR)	3·6†	0 59	0·41	0 83	0 90	
25	S(AD)	2·7†	0 84	0 87	0 89	0 85	AD (severe, soybean, 1 7 years)
26		<0 1	0 91	1 12	0 63	0 89	
27		<0 1	1 13	0 97	0·81	0 68	
28		0·2	0 95	0 87	0 79	0 69	
29	M(AR), B(AD)	<0 1	0·77	1 17	0 78	0 73	
30		<0 1	0·61	0 64	0·72	0 77	
31	F(BA)	<0 1	0·93	0 79	0·67	0 66	
32		0·2	1 09	0 63	0 61	0 54	
33		0 2	1 18	0·96	0 43	0·51	
34		<0·1	0 42	0·47	0 43	0 50	
35		0·2	0·93	0 71	0 39	0 50	
36		<0·1	0 87	0 72	0 48	0 38	
37		0·2	0 90	0 81	0·46	0 45	

B, brother, S, sister; F, father; M, mother, AD, atopic dermatitis, AR, allergic rhinitis, BA, bronchial asthma, WH, wheezy bronchitis.
*Mean of triplicate
†≥0·5 IU/ml for cord blood IgE concentration or ≥1 5 for SI of proliferative responses of CBLs.

greater than 0·5 IU/ml and in three (37·5%) of eight subjects whose SI was greater than 1·5 in proliferative responses of CBLs stimulated twice by ovalbumin or bovine serum albumin (table 2A). In four (50·0%) of eight subjects whose SI was greater than 1·5 in proliferative responses of CBLs stimulated twice by ovalbumin or bovine serum albumin cord blood IgE concentrations were greater than 0·5 IU/ml (table 2B).

Table 2 Relationship between allergic history of the family, cord blood IgE concentrations, and proliferative responses of CBLs stimulated twice by ovalbumin or bovine serum albumin

(A) Allergic history of the family	*Cord blood IgG concentrations (IU/ml)*		*Proliferative responses of CBLs to ovalbumin or bovine serum albumin (SI)*	
	<0·5	*≥0 5*	*<1 5*	*≥1 5*
Negative (26)*	20	6	21	5
Positive (11)†	7	4	8	3
Total	27	10	29	8

(B) Cord blood IgE concentrations (IU/ml)	*Proliferative responses of CBLs to ovalbumin or bovine serum albumin (SI)*	
	<1·5	*≥1 5*
<0·5 (27)†	23	4
≥0·5 (10)†	6	4
Total	29	8

*The numbers in parentheses are the numbers of infants in whom allergic history of the family was negative or positive.
†The numbers in parentheses are the numbers of infants whose cord blood IgE concentrations were less than 0 5 IU/ml or greater than 0 5 IU/ml

ALLERGIC DISORDERS AND SYMPTOMS IN INFANTS

All 37 newborns were followed up for two years. As shown in table 1, atopic dermatitis or atopic dermatitis and wheezy bronchitis developed in seven (18·9%) of 37 subjects. Allergic manifestations in these seven infants are shown in table 1.

RELATIONSHIP BETWEEN VARIABLES FOR PREDICTION AND ALLERGIC DISORDERS IN INFANTS

This is summarised in table 3. The sensitivity and specificity of each variable in the prediction of the development of allergic disorders are also shown in table 3. There was a history of allergy in the family in four (sensitivity 57·1%) of seven infants who developed allergic disorders. Cord blood IgE concentrations were greater than 0·5 IU/ml in three (sensitivity 42·9%) of seven infants who developed allergic disorders. SI was greater than 1·5 in proliferative responses of CBLs stimulated twice by ovalbumin or bovine serum albumin in six of seven infants who developed allergic disorders (sensitivity 85·7%,

$p<0.0005$ compared with non-allergic group) (table 3). In comparison, among the 30 infants of the non-allergic group, seven (23·3%) had positive allergic history of the family, seven (23·3%) had cord blood IgE concentrations greater than 0·5 IU/ml, and only two (6·7%) had an SI greater than 1·5 in proliferative responses of CBLs stimulated twice by ovalbumin or bovine serum albumin. The specificities of positive allergic history of the family, cord blood IgE concentration greater than 0·5 IU/ml, and an SI greater than 1·5 in proliferative responses of CBLs stimulated by ovalbumin or bovine serum albumin were 76·7%, 76·7%, and 93·3%, respectively. As shown in table 4, in all seven infants who developed allergic disorders, cord blood IgE concentrations were greater than 0·5 IU/ml and/or the SI was greater than 1·5 in proliferative responses of CBLs stimulated twice by ovalbumin or bovine serum albumin. The sensitivity and specificity of this combination for prediction were 100% ($p<0.0005$ compared with the non-allergic group) and 76·7%, respectively (table 4).

Moreover, as shown in table 1, four infants (subjects 2, 3 6, and 7) with atopic dermatitis who are sensitive to hens' egg had proliferative responses of CBLs, at least, to ovalbumin, and two infants (subjects 1 and 5) with atopic dermatitis who are sensitive to cows' milk had proliferative responses of CBLs to bovine serum albumin but not to ovalbumin. One patient (subject 25) with atopic dermatitis who is sensitive to soybean had no proliferative responses of CBLs to either ovalbumin or bovine serum albumin (table 1).

Table 3 Relationship between allergic history of the family, cord blood IgE concentrations, proliferative responses of CBLs stimulated twice by ovalbumin or bovine serum albumin, and the numbers of infants who developed allergic disorders for two years

	Allergic history of the family		*Cord blood IgE concentrations (IU/ml)*		*Proliferative responses of CBLs to ovalbumin or bovine serum albumin (SI)*	
	Negative	*Positive*	*<0 5*	*≥0 5*	*<1 5*	*≥1 5*
Allergic disorders developed in infants:						
Non-allergic (30)*	23	7	23	7	28	2
Allergic (7)*	3	4	4	3	1	6‡
Total	26	11	27	10	29	8
Positive rate (%)	29·7 (11/37)		27 0 (10/37)		21·6 (8/37)	
Sensitivity (%)†	57 1 (4/7)		42·9 (3/7)		85 7 (6/7)‡	
Specificity (%)†	76·7 (23/30)		76 7 (23/30)		93 3 (28/30)	
Accuracy (%)†	73 0 (27/37)		70·3 (26/37)		91·9 (34/37)	

*The numbers in parentheses are the numbers of infants who did not develop or developed allergic disorders for two years

†Sensitivity. true positives/(true positives+false negatives); specificity true negatives/(false positives−true negatives) and accuracy. (true negatives+true positives)/total number of cases.

‡$p<0.0005$ compared with non-allergic group.

Table 4 Relationship between the numbers of infants who developed allergic disorders for two years and the combination of cord blood IgE concentrations and proliferative responses of CBLs stimulated twice by ovalbumin or bovine serum albumin

	Cord blood IgE. <0 5 IU/ml and proliferative responses of CBLs. SI<1·5	*Cord blood IgE. ≥0 5 IU/ml and/or proliferative responses of CBLs. SI≥1 5*
Allergic disorders developed in infants.		
Non-allergic (30)*	23	7
Allergic (7)*	0	7‡
Total	23	14
Positive rate (%)	37·8 (14/37)	
Sensitivity (%)†	100·0 (7/7)‡	
Specificity (%)†	76·7 (23/30)	
Accuracy (%)†	81·1 (30/37)	

*The numbers in parentheses are the numbers of infants who did not develop or developed allergic disorders for two years

†Sensitivity: true positives/(true positives+false negatives), specificity true negatives/(false positives+true negatives), and accuracy (true negatives+true positives)/total number of cases

‡$p<0.0005$ compared with non-allergic group.

Discussion

Several investigators have shown that newborn infants with raised IgE concentrations of cord blood are at increased risk of developing allergic diseases.[4–6] Michel *et al*[4] and Magnusson[5] reported that the IgE concentrations of cord blood appeared to be more predictive for the development of allergy in infancy than the family history. Moreover, Iikura *et al* reported that the measurement of specific IgG and IgG_4 in cord blood could be useful in the prediction of the development of allergic diseases and of offending foods.[14] However, several reports showed that a raised cord blood IgE concentration is specific but not sensitive in the prediction of the development of allergic disorders.[5–7] Kjellman and Croner reported that although the specificity was 97%, the sensitivity was 28%,[7] and Magnusson reported that although the specificity was 93%, the sensitivity was 68%.[5] These data indicate that a low cord blood IgE concentration does not exclude the development of allergic diseases.

Allergic disorders that begin early in life are often atopic dermatitis and food allergy such as hens' egg and cows' milk sensitivities. We previously reported that in children with atopic dermatitis who are sensitive to certain foods, there is no significant correlation between the proliferative responses of peripheral blood lymphocytes and radioallergosorbent test to each food allergen, and that the proliferative responses of peripheral blood lympocytes to each food allergen is very useful in the diagnosis of hypersensitivity in food sensitive atopic dermatitis.[9]

In humans, sensitisation in utero was suggested by several investigators.[4 15] In this study, proliferative responses of CBLs to food antigens were measured. Although CBLs stimulated once by ovalbumin or bovine serum albumin showed no proliferative responses in any subject, CBLs stimulated twice by ovalbumin or bovine serum albumin exhibited proliferative responses in some subjects. We utilised the optimum double stimulation times of five and three days with a concentration of 2·5 or 25 μg/ml of each antigen. Our observations provide further evidence that sensitisation is occurring in utero. This would appear to be increasingly important in the genesis of early atopic problems. It may be due to the weakness of in vivo sensitisation by offending allergens in the maternal uterus that CBLs responded to ovalbumin or bovine serum albumin only in double stimulations. The specificity (93·3%) and the sensitivity (85·7%) of the proliferative responses of CBLs in the prediction of the development of allergic disorders were greater than those of the raised cord blood IgE concentrations or the allergic history of the family, respectively. Moreover, the sensitivity was increased by combining the cord blood IgE concentrations and proliferative responses of CBLs to food allergens. The measurement of proliferative responses of CBLs was also able to predict offending allergens. However, Ruiz *et al* report that maternal blood may have contaminated cord blood in 7% of their cases.[8] In a further experiment, proliferative responses of CBLs to each food allergen will be compared with the responses of maternal peripheral blood lymphocytes and the responses of peripheral blood lymphocytes at seven days in the subjects whose CBLs responded to the allergen. Thus, the possibility of maternal blood contamination and the effects on the responses of CBLs will be investigated.

Taken together, our results indicate that the detection of the proliferative responses of CBLs to food antigens is useful in the prediction of not only the development of allergic disorders but also offending allergens. However, as our follow up is only two years, in utero sensitisation is a prediction for the early development of atopic disease but only longer follow up will show whether this holds good for allergic disorders at any age.

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Archives of Disease in Childhood 1992; 67: 1008–1010

Risk of developing atopic disease after early feeding with cows' milk based formula

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Abstract

A follow up of a cohort of 736 healthy full term children with exposure to cows' milk based formula and breast milk from donors on the maternity ward was performed. The children were divided into three exposure groups according to the feeding patterns on the maternity ward. Group 1 received only mother's milk, group 2 mother's milk and human donors' milk, and group 3 received mother's milk, donors' milk and cows' milk based formula. The children were investigated at 7 years of age, by examining their medical files, and at 11 and 14 years, by questionnaires regarding symptoms of atopic disease.

No significant differences between the three groups at follow up were found in the cumulative incidences of atopic diseases. The amount of formula given did not affect the risk of developing atopic disease. Children with a family history of such diseases ran the same risk of subsequent atopic disease whether they were fed formula or breast milk alone. Cows' milk based formula given on the maternity ward does not seem to increase the risk of developing atopic disease.

(*Arch Dis Child* 1992;67:1008–1010)

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Accepted 8 March 1992

The newborn child is immature as regards certain immunological functions and has a low production of secretory IgA. The child receives large quantities of IgA antibodies in mother's milk, some of which are directed against food proteins in the mother's diet. This creates an 'antigen-avoidance system' by preventing contact between the mucosal lining of the newborn's gut and the food given.[1] In animal models the response of the immunological system of the newborn depends on the dose of foreign protein.[2] The newborn infant has a high macromolecule absorption because the gut mucosa is immature. Hence the administration of even small amounts of foreign proteins may result in activation of the immunological system.[3] A minimal amount of cows' milk secreted in breast milk may result in antigen-antibody complexes in the newborn's blood. The role of this process in the genesis of the later development of conditions such as allergies and infections is reviewed elsewhere.[3]

The clinical importance of the early introduction of cows' milk proteins has been extensively studied, but the results have been conflicting.[4–6] Children with a family history of atopic disease have been shown to run a greater risk of developing atopic symptoms when exposed to cows' milk protein than do children without heredity.[7] However, only a few of the studies performed have focused on the very early introduction of cows' milk formula,[7–9] and for ethical reasons such studies have been difficult to perform on term neonates.[7]

The aim of this study was to evaluate the effect of the administration of cows' milk based formula, given in the maternity ward, for later development of atopic diseases.

Subjects and methods

The investigation was performed in Karlskoga, an industrial town in the middle of Sweden with small social class differences and little industrial pollution. All children were born in the town, were nursed on the local maternity ward during 1970, 1973, and 1976, attended the 1st, 4th, and 7th grades at the compulsory school in 1984; a total of 952 children were included. The children's feeding patterns up to the eighth day of life were determined by examining the files from the maternity ward. The children stayed at the maternity ward from birth up to six to eight days of life. Data concerning supplementary feeding to breast milk after leaving the maternity ward was not collected. The feeding patterns were available for 754 children. No data were available for 198 children, mostly because the files from the maternity ward could not be found or because no notes had been made or because the children had been transferred to a regional paediatric centre. The study group therefore consists of healthy full term children without any apparent abnormalities.

The children were divided into three groups based on the neonatal feeding patterns: group 1=mother's milk only (n=219), group 2=mother's milk and human donor milk (n=277), and group 3=mother's milk, human donors' milk, and cows' milk based formula (n=240). Eighteen infants had feeding patterns that diverged from those of the three groups, some did not get mother's milk at all, some received mother's milk and formula but not donor's milk, and they were therefore excluded. A total of 282 infants born in 1970, 215 born in 1973, and 239 born in 1976 were included. At the time of their birth, the feeding routines were based on a fixed feeding schedule with a meal every fourth hour. If the mother did not produce enough milk, formula or human milk from donors was given without regard to a family history of atopic disease. The donors were other mothers on the ward; their milk was not pasteurised and it was stored in a refrigerator for no longer than 24 hours. The formula used was a cows' milk based preparation (Milkotal, Nestlé). No hypoallergenic diets were used. In 1970 only two children received formula, in 1973 there were 35%, and in 1976 there were 68%.

In 1984 the medical files of all the children were examined at the child welfare centres, where all the children were followed up, at the school health units, and at the local hospital. All medical care in the city was provided by the local hospital. When the children were 7 years old the cumulative incidence of asthma, rhinoconjunctivitis, and eczema was determined. The criteria for the diagnosis of asthma was three hospital records showing that the child had had this condition, and for rhinoconjunctivitis and atopic eczema it was the physician's findings at the time of examination.

In 1984 and 1987, questionnaires were sent to the parents about the children's current and previous atopic symptoms, nursing time, family history of atopic disease, etc. Ninety six percent of the parents of 11 and 14 year old children answered the questionnaires. The cumulative incidence of atopic symptoms at 11 and 14 years of age were determined on the basis of the replies. The medical files and the questionnaires were examined without knowledge of the neonatal feeding pattern. The reported time of cessation of breast feeding was validated by notes from the child welfare centre for a subsample (n=47) and was found to be of acceptable quality (r=0·86).

The statistical analyses were based on calculating the crude rate ratio and the 95% confidence interval of the rate ratios.

Table 1 Description of the three milk groups according to birth weight, duration of breast feeding, and family history of atopic disease (n=736)

	Group 1 (n=219)	*Group 2 (n=277)*	*Group 3 (n=240)*
Mean (SD) birth weight (g)	3560 (423)	3521 (509)	3493 (556)
Mean (SD) duration of breast feeding (months)	4 2 (2·9)	4 1 (3 3)	3 9 (3 9)
Family history of atopic disease (%)	33·8	35 0	39 2

Results

The children in the three milk groups were comparable as regards birth weight, duration of breast feeding, and a family history of atopic disease (table 1). The rates of smoking among parents and exposure to animal dander did not differ between the three groups. The cumulative incidence and the crude rate ratios of atopic diseases at the age of 7 years, based on medical files was 9·4% (table 2). The differences between the three milk groups for various types of atopic diseases were not statistically significant.

The cumulative incidence of atopic disease at 7 years of age for children with a family history of atopic disease compared with that for children without a family history is shown in table 3. The incidence was about twice as high in the former group, 14·7% compared with 6·4%. There were no differences in the development of atopic disease between the three feeding groups for children with and without a family history. The cumulative incidence of atopic symptoms at the age of 14 years based on questionnaire responses was 31·4% (table 4). These differences were also

Table 2 Cumulative incidence of atopic disease at the age of 7 years, based on medical files (n=736)

	Group 1		*Group 2*			*Group 3*			*No (%) total*
	No	*Rate ratio*	*No*	*Rate ratio*	*95% Confidence intervals*	*No*	*Rate ratio*	*95% Confidence intervals*	
Asthma	5	1 0	5	0 79	0 2 to 2 7	8	1·48	0·5 to 4 6	18 (2·4)
Rhinoconjunctivitis	9	1·0	10	0 87	0 3 to 2 2	6	0 6	0 2 to 1 7	25 (3 4)
Atopic eczema	9	1·0	13	1 15	0·5 to 2 7	17	1 78	0 8 to 4 0	39 (5·3)
Total									69 (9 4)

Table 3 Cumulative incidence of atopic diseases at the age of 7 years, based on medical files of children with or without a family history for atopic disease (n=736)

	Group 1		*Group 2*			*Group 3*			*No (%) total*
	No	*Rate ratio*	*No*	*Rate ratio*	*95% Confidence intervals*	*No*	*Rate ratio*	*95% Confidence intervals*	
Without family history (n=471)	5	1 0	12	1 66	0 6 to 4 5	12	2 08	0 8 to 5·6	30 (6 4)
With family history (n=265)	11	1 0	15	1 05	0 4 to 2 4	13	0 92	0·4 to 2 2	39 (14 7)

Table 4 Cumulative incidence of atopic disease at the age of 14

	Group 1 (n=213)		*Group 2 (n=190)*			*Group 3 (n=72)*			*No (%) (n=475) total*
	No	*Rate ratio*	*No*	*Rate ratio*	*95% Confidence intervals*	*No*	*Rate ratio*	*95% Confidence intervals*	
Asthma	7	1 0	5	0 80	0 2 to 2 5	3	1·28	0 3 to 5·1	15 (3 2)
Rhinoconjunctivitis	33	1 0	26	0·86	0 5 to 1 5	6	0 50	0 2 to 1·2	65 (13 7)
Atopic eczema	41	1 0	39	1·08	0 7 to 1 8	14	1·01	0 5 to 2 0	94 (19 8)
Total									149 (31 4)

Table 5 Cumulative incidence of atopic disease at the age of 7 years (based on medical files) and 11 years of age (based on questionnaire replies) in relation to the amount of formula given

Amount of cows' milk formula (g)	*No*	*Cumulative incidence number (%)*	
		Atopic disease at 7 years (n=219)	*Atopic disease at 11 years (n=217)*
10–50	60	7 (11·7)	16 (30·8)
60–125	59	6 (10·2)	15 (28·3)
130–250	54	5 (9·3)	16 (31·4)
≥260	37	5 (13·5)	10 (29·4)

not significant To evaluate the possible effect of the amount of formula given on the maternity ward on the subsequent development of atopic disease, the cumulative incidence of atopic diseases at the ages of 7 and 11 is related to the dose of formula given. The figures are summarised in table 5. No statistically significant differences could be found.

In order to evaluate the effect of very early formula feeding on the development of atopic disease, the 217 children in group 3 were divided at 11 years of age into three subgroups, according to the day of life the formula was introduced. These results were: formula introduced days 0–1, 23 (21%) had atopic disease; day 2, 16 (16%); and days 3–8, 25 (20%). There were no significant differences.

Only 18 children received formula before breast milk was introduced. The cumulative incidence among these children at 11 years of age was similar to that in the group as a whole.

Discussion

In this study all the children were breast fed and were thus exposed to factors in their mother's milk that could protect them from developing an atopic disease. As these factors are formed by an interaction of immunological 'forces' between the mother and the child,[1] it was desirable that the children who received donor's milk as a supplement should form a separate follow up group. The outcome of this study is based on data from medical files and questionnaires. In medical files only the more obvious symptoms are noted. More discrete symptoms, if not forgotten, may be reported in questionnaires.

The figures presented in this study for a family history of atopic disease are in good agreement with the results of another Swedish epidemiological study.[10] Atopic symptoms was mentioned in the charts of 9·4% of the 7 year old children and in 31·4% of the 14 year old children. Similarly high incidences of atopic disease are reported in other Swedish studies.[10–13] There is no evidence that the healthy full term children who were excluded because of inadequate information about neonatal feeding differed in any respect that might change our conclusions. The statement that the supplementary food was given in a random way is strengthened by the fact that the frequencies of a positive family history of atopy in the three feeding groups were similar. Furthermore, the debate about the possible harmful effects of foreign proteins given at an early age on the maternity ward had not started at the time of the birth of these children.

In some studies a family history of atopic disease was reported to increase the risk of the subsequent development of atopic symptoms when cows' milk was given on the maternity ward.[7 14] We were unable to confirm these results. A family history of atopic disease increased the risk of developing atopic symptoms from 6·4% to 14·7%, This increase, however, was not affected by the kind of food that was given on the maternity ward. Our numbers are too small to permit conclusions regarding children with two parents with a history of atopic disease. It has been suggested that formula has a blocking effect on the immunological system if given before the first meal of breast milk.[8] In our study only 18 children had received formula before breast milk. These children ran the same risk of developing an atopic disease as did the total group. No difference in the development of atopic disease was seen in relation to the day of life when formula feeding was introduced. Small amounts of formula given in the maternity ward have been believed to result in cows' milk sensitisation, and this could be maintained by the cows' milk protein secreted into the breast milk.[14] Despite the evidence suggesting that small doses of foreign proteins may be more likely than larger ones to provoke sensitisation and the development of atopic disease, our data showed no relationship between the dose of cows' milk formula and the subsequent incidence of atopic disease.[2 15]

Despite rather broad confidence intervals for the relative risk this study suggests that the administration of supplements of cows' milk based formula to healthy breast fed term children on the maternity wards does not increase the risk of developing atopic diseases.

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Newly diagnosed diabetes: a study of parental satisfaction

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Abstract

A national survey of 509 parents of children with newly diagnosed diabetes elicited a 92% response rate, showing that 96% of children were admitted to hospital, 42% staying in hospital longer than one week and 41% received an intravenous infusion. More than 90% of parents expressed satisfaction with the information given at diagnosis, the preparation they received before discharge home, and the outpatient follow up services. Home visits from a diabetes nurse specialist (DNS) were received by 73% of families and 44% reported that the DNS was the most supportive person in the first year after diagnosis. Readmission during the first 12 months after diagnosis was required by 23% of children, more often in the youngest age group. Poor liaison with schools and the lack of diabetes knowledge in teachers were the sources of greatest dissatisfaction.

Children under the care of paediatricians with no specialist interest in diabetes were significantly more likely to be kept in hospital longer at diagnosis and parents were less satisfied with outpatient care and school liaison. The study supports previous recommendations that diabetes nurse specialists are a priority resource in providing support services and that every district should have a paediatrician with a special interest in diabetes and a designated children's diabetic clinic.

(*Arch Dis Child* 1992;67:1011-1013)

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Accepted 13 April 1992

Diabetes in children requires readjustments in family life[1] with parents expressing a need for support and advice.[2] There has been little research evaluating parental satisfaction in the support received by children with diabetes. Challen *et al* asked parents about the support they had received since their child's diagnosis of diabetes mellitus.[3] Comments made by parents were wide ranging and led them to suggest ways in which family support might be improved.

In 1988 a national survey of the incidence of childhood diabetes was undertaken using the active reporting system of the British Paediatric Surveillance Unit.[4] In the same year a working party of the British Paediatric Association (BPA) investigated the services provided for children with diabetes in the UK.[5] The data available from these two surveys formed the basis of this assessment of parental satisfaction with hospital and community services during the 12 months after the diagnosis of diabetes. We were particularly interested in whether there was any association between the level of parental satisfaction and paediatricians' specialist interest.

Subjects and methods

The study sample was selected from the 1988 national survey of 1174 families who returned the original questionnaire. Information was available on the parental social class and education, the age of the child at diagnosis, and the specialist interest of the child's paediatrician. The latter was assessed by the answers given to three key questions: the paediatrician's stated level of interest in diabetes, clinic size, and clinic type. The working party then assigned paediatricians to one of four groups as follows:

(A) Paediatricians fulfilling the following three criteria: (1) specialist diabetologist/endocrinologist or with a major interest in diabetes; (2) caring for more than 40 children with diabetes; (3) seeing children in a designated paediatric diabetic clinic.

(B) Paediatricians fulfilling any two of the above criteria.

(C) Paediatricians fulfilling any one of the above criteria.

(D) Paediatricians not fulfilling any of the above criteria.[5]

The last 509 parents to respond to the initial questionnaire were selected and sent a postal questionnaire. This questionnaire comprised 30 'closed' type questions covering aspects of care at diagnosis, in the outpatients' clinic, at school, and at home. Satisfaction questions were in a four point forced choice format ranging from very satisfied to very dissatisfied. The data was analysed using the Statistical Package for Social Sciences to provide tables and χ^2 calculations using as the variables the child's age, specialist grouping of the paediatrician, and mother's level of education (divided into three groups: none, trade or 'O' levels, 'A' levels, or degree). Assumptions have been made that the mother was the main carer of the child. Only the significant findings are reported.

Results

Questionnaires were returned by 469 (92%) parents. There were 114 (24%) children who were under 5 years at diagnosis, 183 (39%) aged 5 to 10, and 172 (37%) between 11 and 15.

The percentage of children under the care of paediatricians in groups A, B, C, and D were 30%, 21%, 21%, and 16% respectively (12% not known) and evenly distributed with regards to the child's age and the mother's education.

DIAGNOSIS AND MANAGEMENT

A family member was the first to suspect diabetes in 282 (60%) cases and the general practitioner in 128 (27%). There were 452

(96%) children admitted to hospital, 261 (58%) for up to one week, 163 (36%) for one to two weeks, and 27 (6%) for over two weeks, 41% receiving an intravenous infusion. Children under the care of paediatricians in group D were more likely to be kept in hospital longer than one week (χ^2=18·23, df=6, p=0·006) irrespective of the child's age or the mother's education.

Readmission during the first year was required by 110 (23%) children, the majority (81%) only once or twice. Readmission was significantly more likely to occur in the under 5 age group (χ^2=9·64, df=2, p=0·008).

PARENTAL INFORMATION AND SATISFACTION

There were 434 (93%) parents who thought that the information given at initial diagnosis was good or very good, 27 (6%) felt it was poor or very poor, two found it non-existent.

The consultant paediatrician and/or the diabetes nurse specialist (DNS) were reported by 337 (72%) as giving the most useful information on the initial admission. A total of 424 (90%) parents felt very well or quite well prepared to cope with their child on discharge and 425 (91%) were satisfied or very satisfied with the help and information they received in the hospital. The parents of children under 5 years were more likely to feel dissatisfied or very dissatisfied (χ^2=9·22, df=2, p=0·01).

FOLLOW UP

After discharge from hospital two thirds of the children were seen five or more times in the outpatient clinic with almost one third having seven or more visits in the first year. There were 442 (94%) parents who saw the consultant paediatrician in outpatients, but only 345 (74%) saw a DNS and 348 (74%) a dietitian. Only 39 (8%) parents had the option of seeing a social worker at the clinic. Few clinics offered professional psychological support for the family.

There were 422 (90%) parents satisfied or very satisfied with the care and support received in the outpatient clinic. However, 42 (9%) parents were dissatisfied or very dissatisfied and were more likely to be attending the clinics of paediatricians in group D (χ^2=23·93, df=3, p<0·001) where the child was less likely to see the DNS (χ^2=18·87, df=3, p=0·0003) or the dietitian (χ^2=30·13, df=3, p<0·001).

SCHOOLING

Once back at school one third of children had more time off in the year after diagnosis than in the previous year. Of 374 parents 184 (49%) said that a DNS had visited the school; however, 50% of parents were concerned about the lack of knowledge and understanding of diabetes by the teachers. Only 48 (13%) children had many problems with their diabetes at school, the remainder having few or no problems. There were 197 (64%) of 309 parents satisfied or very satisfied with school arrangements while 113 (37%) felt dissatisfied or very dissatisfied. Parents were more likely to feel dissatisfied if under the care of paediatricians in group D compared with those in group A (χ^2=11·96, df=3, p=0·008).

HOME MANAGEMENT

Of 344 (73%) families who received home visits from the DNS, only 141 (41%) said it was on a regular basis.

There were 358 (76%) families who had few or no problems managing their child's diabetes at home, while 101 (22%) had several or many problems; 449 (96%) parents felt confident in looking after their child in the first year, and 346 (74%) families were very satisfied or satisfied with the care and support received at home. Mothers with children under 5 years of age were significantly less likely to be satisfied (χ^2=8·71, df=2, p=0·01); this was true also of mothers with the middle level of education (in trade or with 'O' levels) (χ^2=10·9, df=2, p=0·004).

Some 207 (44%) parents thought the DNS was the most supportive person during the first year; 386 (82%) parents had joined the British Diabetic Association (BDA) and 287 (61%) said that a local support group also existed, although not all attended.

Discussion

Studies of consumer satisfaction with medical care have become an important component of health service research. Consumers are becoming more demanding about the type of care they receive and providers are becoming more attentive to their concerns. Not only is patient satisfaction an integral part of quality of care, but patients who are more satisfied and thus more concerned in their own care will be more likely to comply with treatment regimens and may have better outcomes.[6] Challen *et al* found the most frequent factor related to satisfaction with services was immediacy of access of professional advice.[3] Although our study did not specifically ask about immediate availability of professional help, the parents' high level of satisfaction and confidence suggests that this issue had been well covered by the services. Indeed the most striking finding of this study is the high degree of satisfaction parents had with the information and support they received both as inpatients and outpatients. The satisfaction levels are higher than the 80% quoted in previous studies.[7] However, parents of the younger children were more likely to be dissatisfied and these children were more likely to be readmitted in the first year. This may reflect both the diffculties in this age group and lack of adequate community resources.

As 90% of parents were satisfied with outpatient care presumably they viewed these frequent sessions as educational and supportive. Although 94% of children saw the consultant paediatrician, 26% had no chance of seeing a dietitian or a specialist nurse as recommended recently by the BDA.[8] The recommendation by the BPA working party that clinics for diabetic children should be established in each district[5] was supported by the finding that families attending paediatricians in group D were significantly less likely to be satisfied.

The BDA recommends that 'the specialist nurse and/or dietitian should offer to make appropriate contact with the child's school'. This was followed in only 49% of our study population. Over 50% of parents expressed lack of confidence in the teaching staff and commented on the teachers' lack of knowledge about diabetes. A recent article argues the need for increasing teachers' awareness of chronic medical conditions.[9]

In 1983 Bradbury and Smith assessed the knowledge of teachers who had children with diabetes in their schools.[10] Only 25% had an adequate understanding of diabetes and most of the information came from either the pupil with diabetes or their parents and not from medical or nursing personnel. Most schools have a nurse and doctor and they should, with support from the DNS, take a positive advisory role. The lack of confidence in schools expressed by 36% of parents, is identical to that reported by Challen *et al.*[3]

Satisfaction for support received at home was midway between that of hospital and school. Parents of younger children were the most dissatisfied. Stein and Jessop, studying a group of children with chronic diseases, found a significant beneficial effect of a 'paediatric home care program' on parental satisfaction.[11] Paradoxically Moyer found that 82 parents with access to a DNS needed information on more topics and their level of concern was greater compared with 72 parents who had no access to this service.[2] Watson's study of 78 children with diabetes found that the parents' confidence in caring for their child at home was related to the amount of teaching and discussion they had received in hospital. Parents described the early weeks at home as difficult, associated with feelings of isolation. They would have welcomed supportive visits.[12] Many districts have now established paediatric home care units which offer a flexible service designed to meet the needs of children and families.[13] Currently in the UK there are 46 schemes together with 30 specialist schemes.[14]

The BPA working party found that 19% of UK districts had no DNS service, and in those districts with DNSs only 50% provided their phone numbers. As the parents of the youngest and most vulnerable children appear to be least satisfied with services, it would seem prudent to target this group in support schemes by providing a DNS service in all districts.

This study has shown that children under the care of paediatricians in group D (who have less specialist interest in diabetes) were more likely to spend longer in hospital; their families expressed more dissatisfaction with follow up arrangements and were more likely to attend clinics where no DNS or dietitian was available, and they were less happy with school liaison. These findings support the recommendations made in the BPA working party document that children with diabetes should have access to a paediatric diabetes team working within designated children's diabetic clinics.[5] Such services enhance parental satisfaction which is likely to have beneficial effects on motivation and on outcome.

We would like to thank Novo Nordisk for funding this project and the British Paediatric Surveillance Unit (funded by a grant from The Children Nationwide Medical Research Fund)

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Archives of Disease in Childhood 1992, 67: 1014–1017

Prevention of exercise induced asthma by inhaled salmeterol xinafoate

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Abstract

The effect of inhaled salmeterol xinafoate, a long acting β_2 agonist, on exercise induced asthma was studied in a double blind, crossover, and placebo controlled trial. Thirteen asthmatic children with a fall of at least 15% in their forced expiratory volume in one second (FEV_1) after a standard exercise test on a motorised treadmill, on separate days performed the same test 1, 5, and 9 hours after a single dose of 50 μg salmeterol or placebo. FEV_1 was measured before treatment, and before and for 30 minutes after each exercise test. After placebo the number of children with exercise induced asthma was: 10 at 1 hour, 11 at 5 hours, and 12 at 9 hours. Salmeterol prevented exercise induced asthma in all 13 children studied, at 1, 5, and 9 hours. Mean maximum falls in FEV_1 after exercise were at 1 hour: salmeterol 2·7% and placebo 24·6%, 5 hours: salmeterol 5·3% and placebo 22·7% and 9 hours: salmeterol 3·4% and placebo 26·6%. After salmeterol the mean increase in FEV_1 was 17·8% at 1 hour, 19·6% at 5 hours, and 19·2% at 9 hours. Inhaled salmeterol prevents exercise induced asthma and produces significant bronchodilatation for at least 9 hours.

(*Arch Dis Child* 1992;67:1014–1017)

Exercise is a common problem for children with asthma, who tend to be more physically active than adults. Over 70% of asthmatic children studied with treadmill exercise tests have exercise induced asthma,[1 2] and 98% of children attending an asthma clinic complained of symptoms on exercise.[3]

The airway response to exercise is a measure of indirect bronchial responsiveness; the mechanism is not fully understood but probably involves bronchial smooth muscle cells, mast cells, and neurons[4 5] with the release of mediators.[5–7] This response to exercise has been used to assess the efficacy and duration of action of asthma treatments.[3] Inhaled β_2 adrenoceptor agonists are the most effective drugs for the prevention of exercise induced asthma when taken five to 15 minutes before exercise.[8–10] This protective effect, however, lasts for only two hours in the majority of asthmatics[7 8 11] and the duration varies widely.[8 12]

Salmeterol xinafoate is a long acting β_2 adrenoceptor agonist. It has a polar phenylethanolamine head which binds reversibly to the β_2 receptor.[13] In addition to this it has a long non-polar side chain which is thought to bind to the cell membrane adjacent to the β_2 receptor.[14] It has been shown to inhibit in vitro constriction of airway smooth muscle[15] and the release of mediators from mast cells.[13] It produces prolonged bronchodilatation in adult asthmatic patients.[14] The long duration of effect is attributed to an action of the long non-polar side chain. Salmeterol also ablates both the early and late bronchial reaction and the increase in bronchial responsiveness that follows allergen challenge.[16]

There are no published data on the effect of salmeterol in exercise induced asthma or of its use in children. Our aim was to study the effect of a single dose of inhaled salmeterol on exercise induced asthma in children. It has been shown in previous studies that the degree of bronchoconstriction after exercise is reproducible[1] and does not alter significantly with repetition, at intervals of greater than two hours, during the day.[3] We therefore investigated the response to exercise in a group of asthmatic children 1, 5, and 9 hours after a single morning dose of salmeterol. The study was placebo controlled because placebo has been shown to reduce significantly exercise induced asthma in up to 40% of children.[17]

Methods

TRIAL DESIGN

The study was double blind, randomised, crossover, and placebo controlled. Children attending the paediatric asthma clinic at King's College Hospital who gave a clear history of exercise induced cough or wheeze and who were proficient in spirometry, were recruited. The parents gave informed consent for their children to participate and the study was approved by the hospital ethical committee. We calculated from a previous study of exercise induced asthma in children[1] that to detect a 20% difference in the mean maximum fall in forced expiratory volume in one second (FEV_1) after exercise between salmeterol and placebo with 90% power at the 5% level we would require a sample size of 13 patients.

Each child attended the paediatric respiratory laboratory for an initial exercise test. All medication except inhaled steroids was stopped for at least 12 hours beforehand. FEV_1 was measured in a Jaeger Bodytest reverse plethysmograph, with a capacity of 800 litres, checked against a 1L calibration syringe on each occasion. This system was used because many of the children were already familiar with it, the scale could be easily adjusted for different sized children, and for its convenience in making multiple recordings.

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If the baseline FEV$_1$ was greater than 60% of the mean predicted for the child's height[18] the exercise test was done. This consisted of continuous running on a motorised treadmill for two minutes at 5 degrees upward inclination and a speed of 2·5 kilometres per hour (kph), followed by six minutes at 10 degrees and 5 kph.

Heart rate was measured before and immediately after the running period and then FEV$_1$ was measured every three minutes for 15 minutes and every five minutes for a further 15 minutes. The maximum percentage fall in FEV$_1$ from baseline was calculated. Children who attained a pulse rate of at least 170 beats per minute (bpm) and had a fall in FEV$_1$ of at least 15% after exercise were entered into the study.

The children who fulfilled the entry criteria attended the laboratory on two more occasions, which were not less than four and not more than 10 days apart. On each occasion medication was withheld as before. FEV$_1$ was measured and provided this was within 15% of the previous baseline value the study proceeded.

Either 50 μg salmeterol or placebo were administered as aerosols via a large volume spacer device (Volumatic, Allen and Hanburys[19]). Exercise tests using the same settings as in the initial test and with the same measurements of heart rate and FEV$_1$ were done 1, 5, and 9 hours later.

ANALYSIS OF DATA

Group data was expressed as means and 95% confidence intervals (CI). Parametric analyses were used only when normal distribution of data had been established. The pretreatment values of FEV$_1$ were compared using the paired *t* test. Baseline FEV$_1$ before the initial exercise test and pretreatment FEV$_1$ on the two study days were compared using a two way analysis of variance (ANOVA) with patient and study day as factors. Factors influencing maximum fall in FEV$_1$ after exercise and change in FEV$_1$ after treatment were analysed by multiple regression analysis of patient, pretreatment FEV$_1$, treatment, treatment order, and time point after treatment. The maximum falls in FEV$_1$ after exercise at 1, 5, and 9 hours after salmeterol were compared with placebo using paired *t* tests, including the Bonferroni adjustment.[20] Two way ANOVA was used to compare the maximum falls after exercise 1, 5, and 9 hours after each treatment (salmeterol or placebo) with patient and time after treatment as factors. The change from baseline in values of FEV$_1$ before exercise on each study day and at each time point were compared using two way ANOVA. On the day salmeterol was given, FEV$_1$ before treatment and FEV$_1$ before each of the exercise tests were compared by two way ANOVA. Heart rate before treatment and before each of the exercise tests was analysed for treatment effect using two way ANOVA. For the placebo study day the same analyses were performed.

Table 1 Maximum percentage fall in FEV$_1$ after exercise

Patient No	*1 Hour*		*5 Hours*		*9 Hours*	
	Placebo	*Salmeterol*	*Placebo*	*Salmeterol*	*Placebo*	*Salmeterol*
1	40·6	−3·3	44·2	0·8	39·8	2·3
2	44·8	7·8	31·2	13·5	32·6	12·5
3	32·9	3·5	17·6	2·1	25·5	3·0
4	11·6	8·5	17·5	7·8	18·3	7·2
5	21·6	7·3	15·4	7·3	32·1	0·0
6	41·5	7·2	32·2	6·6	40·4	7·2
7	13·1	−2·2	1·0	0·9	17·8	1·7
8	36·1	4·6	38·8	3·8	44·5	5·4
9	20·8	−1·8	37·5	3·2	29·4	1·6
10	23·7	1·3	21·7	10·5	28·3	5·3
11	2·7	0·0	4·0	2·7	1·4	1·4
12	14·8	0·0	18·6	8·0	20·3	−3·0
13	16·3	1·6	15·2	1·6	14·7	3·6
Mean	24·6	2·7	22·7	5·3	26·6	3·4
Mean difference (95% CI)	22·0 (14·3 to 29·7)		17·4 (9·3 to 25·5)		22·8 (16·0 to 29·7)	

Patients

Thirteen children, five girls and eight boys, aged 8 to 15 (mean 12) years fulfilled the entry criteria and completed the study. All were taking an inhaled bronchodilator as required, two were also taking sodium cromoglycate, seven inhaled steroids, and one theophylline. The children remained well and free of respiratory tract infections or exacerbations of their asthma for the duration of the study.

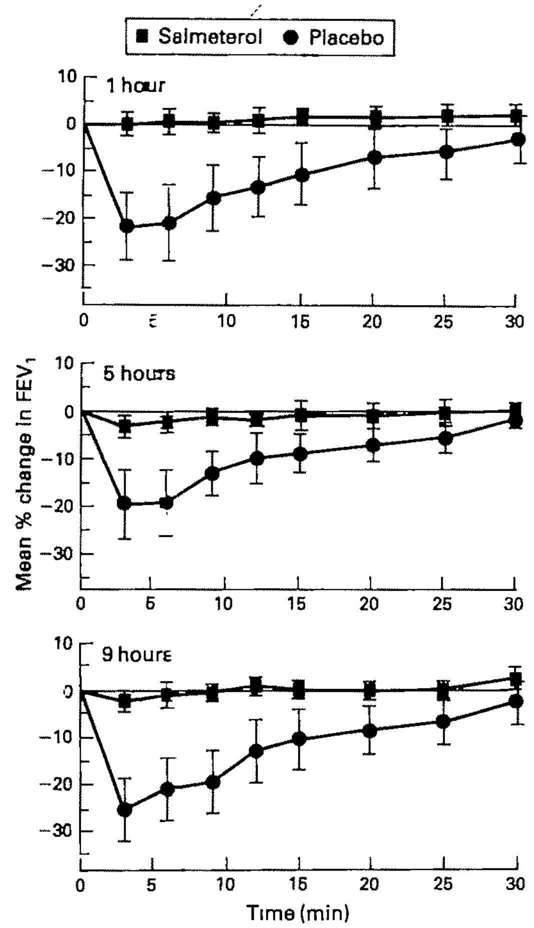
Results

Baseline values for FEV$_1$ at the first visit were from 66% to 104% of predicted (mean 87%). There was no difference between the pretreatment FEV$_1$ values for the two study days ($p=0\cdot24$) and no difference between the initial values for FEV$_1$ on the three visits ($p>0\cdot25$).

The only significant factors for fall in FEV$_1$ after exercise were treatment ($p<0\cdot001$) and patient ($p<0\cdot001$). When the children were treated with salmeterol they had a significantly smaller fall in FEV$_1$ after exercise at 1 hour ($p<0\cdot0003$), at 5 hours ($p<0\cdot0015$), and at 9 hours ($p<0\cdot0003$) than when given placebo. After salmeterol there were no children who had a fall in FEV$_1$ of greater than 15% during exercise tests at 1, at 5 and at 9 hours. After placebo the number of children with a fall in FEV$_1$ of greater than 15% was 10 at 1 hour, 11 at 5 hours, and 12 at 9 hours (table 1). The degree and duration of bronchoconstriction after 1, 5, and 9 hours was very consistent on the day each child was given placebo ($p>0\cdot1$). When salmeterol was given there was complete inhibition of bronchoconstriction at each time point with no diminution of effect over 9 hours ($p>0\cdot05$; figure).

Multiple regression analysis showed the only significant factors for change in FEV$_1$ after treatment were treatment ($p<0\cdot001$) and patient ($p<0\cdot001$). Salmeterol caused a significant increase in FEV$_1$ before exercise at 1, 5, and 9 hours ($p<0\cdot001$). This increase was similar before each exercise test ($p<0\cdot25$). On the placebo study day there was no difference between the baseline and values for FEV$_1$ before exercise ($p>0\cdot25$; table 2).

There was no difference between the heart rates before treatment and before exercise on the salmeterol study day ($p>0\cdot05$) or the placebo study day ($p>0\cdot25$). Mean heart rate before treatment on the salmeterol study day was 88·5 (CI 77·6 to 92·5). The mean heart rates



Change in FEV$_1$ after exercise Bars show 95% CI.

(bpm) before exercise were 89·2 (CI 82·4 to 96·1) at 1 hour, 92·2 (CI 85·8 to 98·5) at 5 hours, and 95·2 (CI 89·8 to 100·7) at 9 hours. Mean heart rate before treatment on the placebo study day was 88·5 (CI 82·4 to 94·6). The mean heart rates before exercise were 85·1 (CI 77·6 to 92·5) at 1 hour, 89·1 (CI 82·8 to 95·3) at 5 hours, and 88·9 (CI 82·8 to 95·0) at 9 hours. No adverse effects were seen.

Discussion

Our results confirm that the technique of repeated exercise tests on a single study day is reproducible. The mean of the individual coefficient of variation for the maximal percent fall in FEV$_1$ after the three exercise tests on the placebo study day was 25·5%; this is similar to previous studies.[1 6 7] There was a placebo effect in some children. The maximal fall in FEV$_1$ was reduced by more than 15% in at least a third of the children after each of the exercise tests on the placebo study day (5/13 at 1 hour, 7/13 at 5 hours, and 7/13 at 9 hours). The effect of placebo on exercise induced asthma has been noted before.[17] In our study the effect on the group as a whole was small and analysis by two way ANOVA of the maximal fall in FEV$_1$ after the initial entry exercise test and after the three exercise tests on the placebo study day did not show a difference ($p>0\cdot01$).

The duration of inhibition of exercise induced asthma in children by inhaled salmeterol xinafoate in this study (at least 9 hours) exceeds that reported in studies of other β_2 agonists. Though the exact mechanisms by which β_2 agonists protect against exercise induced asthma are unclear, it is not apparently related to their bronchodilator effect as bronchodilatation is still present at a time when there is no longer any protective effect against exercise induced asthma.[7 11 21] In our study bronchodilatation was present before each exercise test so it was not possible to exclude bronchodilatation as an alternative cause of the protection from exercise induced asthma. To resolve this question a study with exercise tests at later time points after treatment would be needed. Raised concentrations of inflammatory mediators have been demonstrated after exercise,[22] and inhibition of mediator release is a possible mechanism for the prevention of exercise induced asthma.[7 12 23] Salmeterol has been shown to block the early and late response to inhaled allergen, suggesting an effect extending beyond a protective action on airways smooth muscle.[16]

Tachycardia is a known side effect of β_2 agonists,[24] but in the dose administered there was no significant increase in heart rate before exercise after inhaled salmeterol (two way ANOVA $p>0\cdot05$). Concern has been expressed recently about the regular use of β_2 agonists, particularly as a recent study has found regular use of inhaled fenoterol is associated with deterioration of asthma control.[25] Studies with salmeterol have not shown any deterioration of asthma control[26 27] so the effect observed with fenoterol may not apply to all β_2 agonists.[28] It is unlikely that concern over regular usage of β_2 agonists will apply to their intermittent use on days when vigorous exercise is anticipated.

Asthmatic children, even when receiving regular prophylaxis, may still need pretreatment with an inhaled β_2 agonist to inhibit exercise induced asthma.[6] The main disadvantage of current β_2 agonists is their short duration of action. As organised school sporting activities take place during the afternoon, prevention of exercise induced asthma during these activities relies on asthmatic children taking their treatment at school. A recent study of school teachers in London showed limited understanding of asthma, with only half answering that they should ensure that necessary drugs are taken before games. In addition only half of the teachers would allow asthmatic children to keep their medicines with them.[29] This may

Table 2 Percentage increase in FEV$_1$ before each exercise test (from pretreatment baseline)

Patient No	*1 Hour*		*5 Hours*		*9 Hours*	
	Placebo	*Salmeterol*	*Placebo*	*Salmeterol*	*Placebo*	*Salmeterol*
1	−0·0	16·5	9·0	20·3	9·0	23·1
2	15·9	39·6	0·0	35·9	7·7	39·6
3	1·8	7·5	10·3	2·7	1·2	6·9
4	8·8	30·1	7·6	25·2	13·2	19·0
5	−3·4	14·9	7·7	15·7	10·2	17·3
6	0·0	37·4	5·3	42·1	4·1	37·4
7	11·5	20·4	6·3	25·3	8·3	26·3
8	6·6	44·4	−19·2	29·1	−5·0	47·0
9	8·2	7·8	6·1	21·6	−6·1	21·6
10	−1·7	8·8	0·0	11·7	0·0	10·2
11	1·4	0·0	4·1	6·6	−4·1	1·4
12	10·4	4·4	7·4	10·2	5·9	−1·5
13	0·6	0·0	4·0	3·0	0·0	1·0
Mean	4·6	17·8	3·7	19·6	3·4	19·2
Mean difference (95% CI)	13·2 (4·6 to 21·8)		16·0 (4·9 to 27·1)		15·8 (5·9 to 25·6)	

compound the difficulties facing children who ought to be taking prophylaxis against exercise induced asthma before sport. Physical activities are useful to asthmatic children and appropriate prophylactic treatment by β adrenergic agents will usually permit full participation.[30] In addition efforts should be made to enhance the child's feelings of self worth and avoid feelings of being different from other children.[30]

A single dose of salmeterol xinafoate could be given by a parent in the morning on a day in which sporting activities were anticipated. This would avoid the need for the child to take or be given a dose before exercise. This would also remove any peer pressure attendant on their being seen to take an inhaler at school.

We are grateful to Children Nationwide medical research fund for supporting CPG and to Glaxo Group Research for providing the materials

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Genetic risk for asthma, allergic rhinitis, and atopic dermatitis

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Abstract

In order to explore the genetic risk of a child with a family history of allergies developing asthma, allergic rhinitis, or atopic dermatitis, questionnaires filled in by 6665 families were analysed. The data were collected in a population based cross sectional survey of 9–11 year old schoolchildren living in Munich and southern Bavaria. The relation between asthma, allergic rhinitis, and atopic dermatitis and the number of allergic first degree relatives, and the type of allergic disease was examined. Analyses were done separately for families with single or multiple allergic diseases. In families with one allergic parent the risk of the child developing asthma was increased by asthma in a parent, with an odds ratio (OR) of 2·6 (95% confidence interval 1·7 to 4·0) but not by parental allergic rhinitis with OR 1·0 (0·7 to 1·5) or atopic dermatitis, OR 1·0 (0·6 to 1·6). For allergic rhinitis the highest risk with OR 3·6 (2·9 to 4·6) was observed with allergic rhinitis of one parent, apparently lower for asthma of one parent, OR 2·5 (1·6 to 4·0) or atopic dermatitis, OR 1·7 (1·1 to 2·5). Children with parental atopic dermatitis had a high risk for atopic dermatitis, OR 3·4 (2·6 to 4·4), compared with children with parental asthma, OR 1·5 (1·0 to 2·2), or parental allergic rhinitis, OR 1·4 (1·1 to 1·8). Risk factors in families with combined allergies of two relatives (parents and siblings) were analysed separately for the different combinations. These results support the hypothesis that asthma, allergic rhinitis, and atopic dermatitis are multifactorial diseases brought about by various familial and environmental influences.

(*Arch Dis Child* 1992;67:1018–1022)

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Environmental and hereditary factors are the most important causes of allergies. Little is known about the interaction between genetics and environment and how they influence the manifestation and severity of allergies.

In 1923, Coca and Cooke introduced the concept of atopy to describe allergies of a familial or hereditary nature, which included asthma, allergic rhinitis, atopic dermatitis, urticaria, and food allergies.[1] Whereas in the past recessive and dominant models were discussed,[2] [3] the results of studies in the last 30 years implicate a multifactorial determination.[4–7] The variability of manifestation and severity, the polymorbidity, and the different organ systems involved make it difficult to locate the hereditary base and its molecular genetic mechanisms.[8]

Because of the small number of cases involved in many of the studies and the fact that overlapping effects of multiple diseases in the families were not taken into consideration,[9–13] it has not to date been possible to determine clearly the risk factors for different atopic family situations.

A population based epidemiological survey with a high number of cases should permit a more differentiated examination of the risk due to heredity. The selection of subgroups with a homogeneous allergic family situation allows the estimation of individual risk factors.

The Munich Asthma and Allergy Study is a cross sectional study to determine the prevalence of allergic and asthmatic diseases in schoolchildren in Bavaria. The relationship between atopic diseases of the parents and siblings and the risk of the investigated child developing an allergic disease such as asthma, allergic rhinitis, or atopic dermatitis is analysed with the data from questionnaires completed by 6665 families.

Methods

The data reported in this paper were collected as part of the Munich Asthma and Allergy Study from October 1989 to July 1990. This survey comprised 9349 schoolchildren aged 9 to 11 years, including all fourth grade children in 118 primary schools in Munich and 65 schools in southern Bavaria. The schools in the rural districts were selected for lower air pollution. Questionnaires were sent home from school with the children, answered by their parents, returned to school, and collected by the investigators. The response rate was 88% (8204 questionnaires). This was an informed consent study approved by the ethics commission of the 'Bayerische Landesarztekammer'.

QUESTIONNAIRE

Both current and previous allergic diseases of the child and its relatives were evaluated using a total of 58 questions. The questionnaire was standardised according to the recommendation of the American Thoracic Society and supplemented by some of our own questions.

Information given by the parents that a physician had diagnosed asthma at least once or there had been multiple episodes of wheezy bronchitis ('spastische, asthmoide Bronchitis') was taken as representing asthma. Allergic rhinitis was used synonymously with hay fever. Eczema, neurodermatitis, or itching skin lesions in typical locations were interpreted as atopic dermatitis.

The question 'Did you or a family member ever suffer from one of the following diseases?' was answered separately for the parents, siblings, and grandparents by means of a chart which was divided into sections for bronchial asthma, allergic rhinitis, and atopic dermatitis. Familial allergy was taken to exist when it was stated that at least one family member had at some time asthma, allergic rhinitis, or atopic dermatitis. To estimate the risk of developing asthma, allergic rhinitis, or atopic dermatitis only the data of first degree relatives, parents and siblings, were included.

Because of possible language difficulties and ethnic differences, only questionnaires from German children were considered for evaluation. The response rate of the German children could be estimated only indirectly. In all the primary schools in Munich (from first grade to fourth grade) 24% of children and in southern Bavaria less than 5% are non-German. Considering these figures the response rate for German children was about 89%. The child's sex, nationality, place of residence (Munich/southern Bavaria), parents' education, the number of cigarettes smoked at home, and the person who filled in the questionnaire were analysed as possible confounding variables.

STATISTICS

Only data of first degree family members were included, the grandparents' allergies were not taken into consideration. In analysing the effect of an allergic disease of a sibling or of more than two allergic first degree relatives, children who had no siblings were excluded. To avoid the overlapping effects of multiple genetic disposition, we analysed the genetic risk of different family histories in successive steps. Firstly, additional allergic diseases of other first degree relatives were excluded and the prevalence of the different diseases in children with a positive family history involving one family member was compared with children whose first degree relatives had no atopic disease. Secondly, only single allergic diseases in one parent were evaluated. Thirdly, the effect of different combinations of two allergic diseases in two first degree relatives was estimated.

The risk of an allergic family history is given as an odds ratio (OR) with the corresponding 95% confidence interval (CI). Frequencies were compared for their statistic significance with the χ^2 test. All analyses were carried out with SAS 5·18.

Results

The analysis was based on a total of 6665 questionnaires filled in by Germans, as defined by the nationality of the examined child. The 1539 foreign children were a heterogenous group, of whom 31% (470) were Turkish, 29% (443) Yugoslavian, and 41% (626) were from elsewhere. There were significant differences between German and non-German children in the prevalence of asthma, allergic rhinitis, and atopic dermatitis.[14]

A history of bronchial asthma, allergic rhinitis, and atopic dermatitis of at least one family member (parents, siblings, and grandparents, all with lifetime prevalence) was reported in 47% (3160) of the German families. Including only data from parents and siblings, 40% (2650) had a positive family history. In 15% (1024) of the families there was more than one allergic disease—that is, one or more first degree relatives suffered from one or more allergies. A total of 27% of the children (1776) had one parent suffering from one atopic disease. Allergy of both parents was reported in 4% (241) of the families and 3% (171) had more than two first degree relatives with atopic disease.

Children with atopic disease (asthma, allergic rhinitis, or atopic dermatitis) had a positive family history (first degree relatives) in 55% of cases compared with 35% in children without an atopic disease (p<0·001). The cumulative prevalence of allergies increased with the number of atopic first degree relatives. An allergy of both parents was associated with an allergy in the child in 56% of cases (77/137). There was no difference if the parents had the same type of allergic manifestation (55%, 45/82). In families with more than two allergic first degree relatives, 67% (109/163) of the children had an allergic disease.

The prevalence of asthma, allergic rhinitis, and atopic dermatitis was associated with the number of allergic family members (table 1). However, differentiation between the types of allergic disease in families with one allergic parent showed that the risk of asthma rose only if asthma was present in a parent, rather than allergic rhinitis or atopic dermatitis (table 2).

Allergic rhinitis was seen in 16% of the children with one allergic parent, in 25% if both parents had an allergy, and in 28% with more than two allergic family members (table 1). In families with one atopic parent, allergic rhinitis of the child was most frequent if a parent also had allergic rhinitis (table 2).

Atopic dermatitis similarly increased with the number of allergic family members, from 26% with one parent suffering from an allergy, to

Table 1 Prevalence of asthma, allergic rhinitis, and atopic dermatitis in relation to the number of first degree relatives with an allergic disease. Results are number (%)

Family history	*Asthma*	*Allergic rhinitis*	*Atopic dermatitis*
No allergic family history	257/3995 (6)	240/3984 (6)	553/3690 (15)
Allergic disease of.			
One sibling	47/553 (9)*	56/555 (10)***	115/520 (22)***
One parent	109/1279 (9)**	207/1280 (16)***	317/1219 (26)***
Both parents	23/146 (16)***	36/146 (25)***	55/137 (40)***
More than two first degree relatives	30/170 (18)***	47/170 (28)***	75/162 (46)***

Significance in relation to the group with no family history of allergies, *p<0·05, **p<0·01, ***p<0·001

Table 2 Prevalence of asthma, allergic rhinitis, and atopic dermatitis in relation to the type of allergy of one parent with an allergic disease Results are number (%)

Family history	*Asthma*	*Allergic rhinitis*	*Atopic dermatitis*
No allergic family history	257/3995 (6)	240/3984 (6)	553/3690 (15)
One parent with			
Asthma	34/252 (13)***	38/251 (15)**	51/237 (22)**
Allergic rhinitis	63/783 (8)	152/786 (19)***	170/751 (23)**
Atopic dermatitis	35/402 (9)	49/401 (12)***	149/381 (39)***

Significance in relation to the group with no family history of allergies, *p<0·05, **p<0·01, ***p<0·001

40% with both parents allergic, and 46% in families with more than two allergic subjects. With regard to the type of allergy, the highest risk for atopic dermatitis was observed when a parent also had atopic dermatitis (39%), while it was evidently lower for allergic rhinitis (23%) or asthma (22%) (table 2).

In comparing the prevalence of allergies associated with different types of parental diseases (table 2) we excluded allergies of other family members. In calculating the OR (tables 3–5) of the children with parents, who had different allergic diseases, only parents with a single allergy were compared with families without allergies. This correlation is shown separately for boys and girls. For each disease the highest risk for a parental allergy of the same type was analysed differentiating between the influence of the mother and the father.

Table 3 Child's asthma in relation to one allergic disease of one of the parents and exclusion of additional allergic diseases of first degree relatives. Results are number (%)

Family history	*Boys*	*Girls*	*Total*
No allergic family history	149/1914 (8)	108/2080 (5)	257/3994 (6)
One parent with asthma	14/89 (16)	11/82 (13)	25/166 (15)
OR (95% CI)	2·2 (1·2 to 4·0)	2·8 (1·5 to 5·5)	2·6 (1·7 to 4·0)
Mother with asthma	4/51 (8)	5/47 (11)	9/98 (9)
OR (95% CI)	1·0 (0·4 to 2·8)	2·2 (0·8 to 5·6)	1·5 (0·7 to 2·7)
Father with asthma	10/38 (26)	6/35 (17)	16/73 (23)
OR (95% CI)	4·2 (2·0 to 8·9)	3·8 (1·5 to 9·3)	4·4 (2·5 to 7·8)
One parent with allergic rhinitis	29/329 (9)	14/326 (4)	43/649 (7)
OR (95% CI)	1·1 (0·8 to 1·7)	0·8 (0·5 to 1·4)	1·0 (0·7 to 1·5)
One parent with atopic dermatitis	10/150 (6)	9/146 (8)	19/302 (6)
OR (95% CI)	0·8 (0·4 to 1·5)	1·2 (0·6 to 2·4)	1·0 (0·6 to 1·6)

Table 4 Child's allergic rhinitis in relation to one allergic disease of one of the parents and exclusion of additional allergic diseases of first degree relatives. Results are number (%)

Family history	*Boys*	*Girls*	*Total*
No allergic family history	156/1910 (8)	84/2074 (4)	240/3984 (6)
One parent with allergic rhinitis	76/331 (23)	49/327 (15)	125/668 (19)
OR (95% CI)	3·4 (2·5 to 4·5)	4·2 (2·9 to 6·1)	3·6 (2·9 to 4·6)
Mother with allergic rhinitis	48/194 (25)	31/192 (16)	79/386 (21)
OR (95% CI)	3·7 (2·6 to 5·3)	4·6 (2·9 to 7·1)	4·1 (3·1 to 5·4)
Father with allergic rhinitis	28/137 (20)	18/135 (13)	46/272 (16)
OR (95% CI)	2·9 (1·8 to 4·5)	3·6 (2·1 to 6·3)	3·0 (2·1 to 4·3)
One parent with asthma	15/88 (17)	9/82 (11)	24/170 (14)
OR (95% CI)	2·3 (1·3 to 4·1)	2·9 (1·4 to 6·0)	2·5 (1·6 to 4·0)
One parent with atopic dermatitis	18/159 (11)	11/146 (8)	19/305 (10)
OR (95% CI)	1·4 (0·9 to 2·1)	1·9 (1·0 to 3·7)	1·7 (1·1 to 2·5)

Table 5 Child's atopic dermatitis in relation to one allergic disease of one of the parents and exclusion of additional allergic diseases of first degree relatives. Results are number (%)

Family history	*Boys*	*Girls*	*Total*
No allergic family history	248/1766 (14)	305/1924 (16)	553/3690 (15)
One parent with atopic dermatitis	56/146 (38)	53/143 (37)	109/289 (38)
OR (95% CI)	3·8 (2·7 to 5·5)	3·2 (2·2 to 4·5)	3·4 (2·6 to 4·4)
Mother with atopic dermatitis	44/102 (43)	38/98 (39)	82/200 (41)
OR (95% CI)	4·6 (3·1 to 7·0)	2·4 (1·9 to 3·2)	3·9 (2·9 to 5·2)
Father with atopic dermatitis	12/44 (27)	15/45 (33)	27/89 (30)
OR (95% CI)	2·3 (1·2 to 4·5)	2·7 (1·4 to 5·0)	2·5 (1·5 to 3·9)
One parent with allergic rhinitis	56/320 (18)	70/310 (23)	126/330 (20)
OR (95% CI)	1·3 (0·9 to 1·8)	1·5 (1·2 to 2·1)	1·4 (1·1 to 1·8)
One parent with asthma	12/83 (14)	21/77 (27)	33/160 (21)
OR (95% CI)	1·0 (0·5 to 1·9)	2·0 (1·2 to 3·3)	1·5 (1·0 to 2·2)

Table 6 Risk of asthma, allergic rhinitis, and atopic dermatitis in families with two first degree relatives with an allergic disease. Results are number (%)

Family history	*Asthma*	*Allergic rhinitis*	*Atopic dermatitis*
No allergic family history	257/3995 (6)	240/3984 (6)	553/3690 (15)
Two first degree relatives with allergic rhinitis/atopic dermatitis	18/144 (13)	27/144 (19)	42/135 (31)
OR (95% CI)	2·1 (1·2 to 3·5)	3·6 (2·3 to 5·6)	2·6 (1·8 to 3·7)
Allergic rhinitis/asthma	14/67 (21)	15/67 (22)	24/63 (38)
OR (95% CI)	3·8 (2·1 to 7·0)	4·5 (2·5 to 8·1)	3·5 (2·1 to 5·9)
Atopic dermatitis/asthma	9/47 (19)	9/46 (20)	14/41 (34)
OR (95% CI)	3·4 (1·6 to 7·2)	3·8 (1·8 to 8·0)	2·9 (1·5 to 5·6)
Asthma	10/38 (26)	6/38 (16)	9/35 (26)
OR (95% CI)	5·2 (2·5 to 10·8)	2·9 (1·2 to 7·1)	2·0 (0·9 to 4·2)
Allergic rhinitis	28/235 (12)	63/235 (27)	64/223 (29)
OR (95% CI)	2·0 (1·3 to 3·0)	5·7 (4·2 to 7·8)	2·3 (1·7 to 3·1)
Atopic dermatitis	22/174 (13)	21/174 (12)	71/168 (42)
OR (95% CI)	2·1 (1·3 to 3·4)	2·1 (1·3 to 3·4)	4·1 (3·0 to 5·7)

Only asthma in one parent represented a risk factor for the child to develop asthma, not allergic rhinitis or atopic dermatitis (table 3). Only asthma in the father was associated with a significantly increased prevalence and OR. As expected asthma was more frequent in boys, but the risks represented by the OR were comparable with those of girls.

By excluding multiple allergies of a parent, the strongest difference was observed for the effect of atopic dermatitis in a parent. Isolated parental atopic dermatitis was associated in 6% of cases with asthma in the child, while asthma was observed in 9% of the children (table 2) with possible additional allergies of a parent.

The highest risk for allergic rhinitis (table 4) was observed in children of parents with allergic rhinitis. The influence of the mother was a little stronger than that of the father. The risk increased slightly with parental asthma and atopic dermatitis. A higher prevalence of allergic rhinitis was observed in boys, while girls had higher OR.

Similar results were observed for atopic dermatitis in the child (table 5). Asthma and allergic rhinitis in the parents were associated with slightly higher risk, but the relationship between parental asthma and atopic dermatitis did not achieve statistical significance. Children of parents with atopic dermatitis had the most marked disposition for it, with increased OR if the mother was affected.

RISK FACTORS FOR COMBINED ALLERGIES OF TWO FAMILY MEMBERS

The risk produced by combined allergies of two family members is illustrated in table 6. In all of these allergic diseases, the idiotypic combination resulted in the highest frequency of this allergy. The combined asthmatic disease of two first degree relatives was associated with an OR of 5·2 (95% CI 2·5 to 10·8) for asthma. The combination of asthma and allergic rhinitis showed the highest predisposition for all three allergic diseases.

Allergic rhinitis or atopic dermatitis alone did not constitute risk factors for asthma (table 1). The combination of both was associated with an increased risk for asthma, but this was lower than in combination with an asthmatic disease of one relative.

CONFOUNDERS

The rate of reported atopic dermatitis and allergic rhinitis in the family varied greatly ($p<0·001$) according to education, parental smoking habits, nationality, and place of residence. In families where the parents gained the school leaving final qualification, more family histories of atopic dermatitis or allergic rhinitis were reported (41%) than in families where the parents had an elementary school qualification (23%). This was also true in households without cigarette smokers (36%) as opposed to families with smokers (27%) and was more so in families living in Munich (33%) rather than in southern Bavaria (30%). The same results were noted more often in German families (36%) than in families of other nationalities. There was no significant difference for the rate of reported asthma cases in the family in the different groups.

To estimate the effect of the different confounding variables, the OR for allergies in the child having one family member with an allergic disease was determined in different subgroups. There was no statistically significant difference between boys or girls, whether living in Munich or southern Bavaria, with parents smoking at home or not, whether the questionnaire was filled in by the father or the mother, and between the different standard of parents' education. In nearly all of these subgroups, an OR of about 2 was observed.

Discussion

This population study showed that 40% of the children had an allergic family history and if grandparents were included this figure rose to 47%. It is hence necessary to differentiate between hereditary risk factors. As 15% of the families reported combined allergies, it is important to avoid the overlapping effects by excluding additional allergies in each case. This restriction appreciably reduces the number of the children included in the different evaluations.

Data collected from questionnaires always suffer from various problems. The information given about a child or family member's atopic disease relies on memory and retrospective interpretation by the person who answered the questionnaire. However it is not possible to diagnose asthma, allergic rhinitis, or atopic dermatitis by means of a single examination of the child, because these allergic diseases occur mostly episodically. Nevertheless questionnaires offer a unique opportunity to collect information from a large and representative group in the population. As this survey comprised only chidren aged 9 to 11 years, the different groups are very comparable. It should be noted that the estimated risk for an allergic disease is valid for this age group and could vary for older children.

Earlier studies on allergic inheritance which also determined the prevalence of a family history of allergic disease in individuals with and without allergies, reported a positive family history in 40 to 80% of individuals with an allergic disease compared with 20% or fewer of individuals without an allergic disease.[2 15] Our observation that 35% of children without a reported allergic disease have a positive family history is in keeping with a surprisingly high number of children with an allergic family history.

Studies evaluating the genetic role in allergies often differentiate only between families with and without atopic diseases or take only the number of atopic family members into account.[16 17] Furthermore, investigations which distinguished between the genetic risk of different atopic diseases did not consider the effect of combinations of multiple allergies.[6 12 18 19]

In families with single allergic disease of one parent only asthma, not allergic rhinitis, is a predisposing factor for asthma in the offspring. A longitudinal study in a cohort of children aged 5–9 years observed an increase of the relative risk only for parental asthma.[20] On the other hand, asthma of the mother or the father raises the risk of allergic rhinitis. This one sided relationship supports the hypothesis that allergic rhinitis could be a minor form of bronchial asthma. This is in accordance with the results of a follow up study of college students demonstrating an increased risk of developing asthma for persons with allergic rhinitis.[21]

The prevalence of asthma is higher in boys than in girls, but the risk factors of parental asthma are comparable for both sexes. The finding of a study of 4–6 year old children in New Zealand that parental asthma and atopic dermatitis are only associated with asthma in boys could not be confirmed by our data.[6 18]

The differentiation between allergies of the mother and of the father shows that for asthma in the child only paternal asthma has a strong influence, while for allergic rhinitis and atopic dermatitis the influence of the mother is more decisive. The estimated differences between the influence of the mother and of the father must be interpreted with caution, as 80% of the questionnaires were filled out by mothers. Allergies of the mother are probably over-represented and allergies of the fathers may include more of the acute and severe type.

A cross sectional study of atopic disease in 1325 school entrants found that children whose parents have an identical type (respiratory or skin) of atopic disease more frequently develop an atopic disease (72%) than children with non-identical types of allergies in the parents (21%).[16] We could not find a difference in the prevalence of allergies between the whole group of children with both parents allergic (56%) and children of parents with an identical type of allergic manifestation (55%). But children with two allergic family members with an identical type of allergy have the highest risk of developing that type of allergy. Combinations with different types of allergies do not show a clear relationship to one form of allergy. Additive effects also increased the risk for other types of allergic manifestations.

The proved relationship between atopy of a sibling and atopy of the examined child, which exists independently of parental disease, cannot be explained by a simple hereditary model. The increase in prevalence of allergies in children with one affected sibling and no reported parental disease and the additional increase with three or more family members compared with the group with both parents allergic could be explained by an incomplete genetic penetrance.

Various other types of studies have provided additional insight into the genetic basis of allergies. The results of case-control studies,[11–13] which are based on clinical diagnosis, support the relationship between parental atopy and allergic disease, but due to the small numbers of cases they do not allow differentiation of family allergies.

The differences between monozygotic and dizygotic twins and a tendency for the same type of manifestations as evaluated in a large twin study provides evidence for the genetic nature of atopy.[5] Concordance rates for asthma and allergic rhinitis of monozygotic twins reared apart are quite similar to those of twins reared together, suggesting a substantial genetic component for the development of asthma and allergic rhinitis.[22] But twin studies are unable to identify the pattern of transmission.

Investigations of bronchial hyperreactivity using the methacholine test in healthy family members of asthmatics and in twins support the hypothesis of a separate transmission of hyperreactivity,[23–25] which corresponds with the finding of a separate transmission of asthma. Family studies of serum IgE concentrations show a clear concordance,[17 19] and a genetic determination in the form of an IgE regulating gene has been suggested.[3] Investigations in extended families have suggested that the propensity to produce IgE in response to common, usually inhaled, allergens is inherited as an autosomal dominant linked to chromosome 11.[26 27] But the clinical expression depends on interaction with other factors which may be, to some extent, also genetic. The concentration of IgE in an infant's cord blood has been found in many studies to predict the allergic predisposition of the child. Presumably the cord blood IgE concentration is a reflection of the genetic risk of developing atopic disease.[15] Recent data about the IgG immune responsiveness to grass pollen allergen suggest that it is strongly associated with a specific HLA sequence.[28]

In the clinical situation it is not so important to decide whether genetic transmission is dominant, recessive, or polygenic but to estimate the increased risk in an allergic family constellation. The distinction between defined allergic family situations in this study allows a differentiated statement about the risk in certain family situations, as well as the prediction of the probable type of allergy.

Although various investigations have shown the role of genetic factors in allergies, it should be kept in mind that 23% of the children without any familial disposition also develop allergies. The study of this group of children would be of special interest in exploring the role of environmental factors.

This study was supported by the 'Bayerischen Staatsministerium fur Landesentwicklung und Umweltfragen' We would like to thank Dr E Frhr von Loeffelholz-Colberg, Professor Dr W Lehmacher, and Dr T Nicolai for planning and supervising this study; all 182 participating schools for their support of the study, as well as the children and their parents, whose commitment was essential for the survey

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Early immune responses to *Dermatophagoides pteronyssinus* and atopic predisposition

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Abstract

Responses to the house dust mite during infancy may be important determinants of asthma in susceptible individuals. This study assessed early IgG subclass antibody responses to *Dermatophagoides pteronyssinus* in children of atopic parents. Sixteen atopic and 15 non-atopic children were selected from a birth cohort, and atopic status was established according to follow up over the first two years. IgG_1 and IgG_4 antibodies to *D pteronyssinus* were measured by enzyme linked immunosorbent assay at 7 days and 3, 6, 12, and 24 months. In all children *D pteronyssinus* IgG_1 fell at 3 months (indicating maternal antibody loss), rose progressively to 12 months, and waned at 24 months. *D pteronyssinus* IgG_4 was only detectable at 7 days. Children who were atopic by 2 years and therefore at greater risk of asthma, tended to have higher *D pteronyssinus* IgG_1 at 6 and 12 months. These data suggest greater exposure or responsiveness to dust mite during infancy than in the second year.

(*Arch Dis Child* 1992;67:1023–1026)

House dust mite sensitivity has long been associated with asthma.[1] A causal relationship has been inferred by the influence of the degree of mite exposure on the prevalence of asthma.[2 3] Exposure during infancy may be particularly important in determining subsequent sensitisation to aeroallergens.[4] Children with mite sensitivity are more likely to have been born in a season when mite counts were high,[5 6] and higher levels of mite exposure in infancy have recently been reported among children who have persistent wheezing at 11 years.[7]

While much research has concentrated on measuring mite exposure, it is the individual response to this 'allergen load' that determines whether sensitisation ultimately occurs. There may be threshold levels of exposure for sensitisation[1] but individuals with a similar genetic predisposition to atopy need not produce analogous immune responses to the same allergen load.

During the first year of life children are capable of mounting IgE antibody responses but they are usually to ingested allergens.[8 9] IgE and IgG responses to aeroallergens are reported to be comparatively uncommon before the second year of life.[8] It would be difficult to reconcile the importance of mite exposure during infancy with an apparent lack of immune responsiveness to the allergen at this time. We have recently demonstrated IgG_1 subclass antibodies to the dust mite, *Dermatophagoides pteronyssinus*, during the first year in most members of a group of 'unselected' children.[10] The discrepancy with previous findings may be explained by our use of an enzyme linked immunosorbent assay (ELISA) with whole *D pteronyssinus* extract instead of a radioimmunoassay for antibody to *D pteronyssinus* I.[8] The latter assay was probably less sensitive as antibodies to *D pteronyssinus* I may not represent the majority of dust mite antibodies at this age; they apparently constitute less than half of newly generated IgE antibodies to *D pteronyssinus* in children.[11]

The present study aimed to measure IgG subclass antibody responses to whole *D pteronyssinus* by ELISA in the first two years in subjects selected from a large cohort of children with a predisposition to atopy. The responses were compared between children with the most obvious evidence of atopy during the first two years, who were at greater risk of subsequent asthma,[12] and those who were most clearly non-atopic despite their predisposition.

Subjects and methods

COHORT DETAILS

All cohort members had been term neonates born between September 1987 and July 1989 in the Camberwell Health Authority. They had been identified by a history of atopic disease in both parents on antenatal questionnaires. If informed parental consent was obtained and atopy could be confirmed in at least one parent by a positive skin prick test, the infants were enrolled.[13]

They were assessed initially on day 7 when a blood sample was taken, and then at 3, 6, 12, and 24 months to document atopic disease, perform skin prick tests, and obtain further blood samples. Additional examinations were made when coughs or suspicious rashes were reported.

Eczema diagnosed according to the guidelines of Hanifin and Rajka[14] but modified for infants,[15] wheezing on at least two separate occasions, and a history of recurrent immediate food reactions were each regarded as evidence of atopic disease.

Skin prick tests to dust mite (*D pteronyssinus*), cows' milk, hens' eggs, mixed grass pollens, cat fur (Bencard), mixed moulds (Dome/Hollister-Stier), and histamine 1 mg/ml and diluent control solutions (Bencard) were performed on the back in children and the forearm in parents. A weal after 15 minutes at least 2 mm in children, or 3 mm in adults, greater than that

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Accepted 10 April 1992

caused by the negative control was considered positive.

Sera were stored at −20°C and subsequently analysed for total serum IgE antibody by an ultrasensitive ELISA[16] in 7 day sera and by conventional two site ELISA[17] in all other samples. Undetectable concentrations were assigned a value of 0·01 IU/ml and the geometric mean and SD were calculated for each age group, although 7 day concentrations continued to have a very skewed distribution after log transformation.

The ethical committee of King's College Hospital had approved the method of follow up and all procedures.

SUBJECT DETAILS

Eighty of the original cohort completed the two year follow up. The first 16 (eight girls) classed as atopic and the first 15 (seven girls) considered non-atopic were selected for the study. The number of subjects was limited so that all samples from each age could be assayed together on a single microtitre plate thus eliminating interassay variability.

Children classed as atopic had: (i) positive skin tests to any allergen and (ii) evidence of atopic disease. Children were considered non-atopic if they met all of the following three criteria: (i) negative skin tests, (ii) a total IgE concentration less than 0·5 IU/ml at 7 days and below the geometric mean plus 1 SD at any other age, and (iii) no evidence of atopic disease.

Of the 16 atopic children 11 had suffered with eczema (fig 1) and five had given positive skin tests to *D pteronyssinus*.

LABORATORY MATERIALS

Nunc Immuno (MaxiSorp F96) microtitre plates were purchased from Gibco Ltd, horse serum from Sera Lab Ltd, Tween 20, alkaline phosphatase labelled rabbit antimouse IgG and *p*-nitrophenyl phosphate (PNP) from Sigma Ltd and IgG subclass-specific mouse monoclonal antibodies (clones NL16-IgG1, RJ4-IgG4 and 8a4-IgG) from Oxoid Ltd. Freeze dried whole dust mite extract (*D pteronyssinus*) was a kind gift from Dr R Whal (Allergopharma, Reinbeck, Germany).

IgG SUBCLASS ASSAYS

IgG$_1$ and IgG$_4$ antibodies to *D pteronyssinus* were measured by a two site ELISA[18] in sera from 7 days, and 3, 6, 12, and 24 months in all 31 children. Incubation volumes were 50 µl and temperatures were 4°C unless stated otherwise. There were three washes with phosphate buffered saline (PBS) containing 0·05% Tween 20 between each incubation. The assay diluent was PBS containing 0·5% Tween 20 and 0·5% normal horse serum. Briefly, the microtitre plates were coated overnight with 10 µg/ml *D pteronyssinus* extract in pH 9·6 carbonate/bicarbonate buffer. The test sera, diluted 1/50, were added, in duplicate and incubated for two hours. There followed in sequence one hour incubations with monoclonal IgG$_1$ or IgG$_4$ (1/1000) and alkaline phosphatase-labelled antimouse IgG (1/300). Finally, 100 µl of the substrate, PNP (1 mg/ml in pH 9·8 diethanolamine buffer) were added and after one hour at room temperature, the colour reaction was stopped with 50 µl 3M sodium hydroxide and the optical density read at 405 nm in a Titertek multiskan plate reader (Flow Labs). Antibody concentrations were derived from a standard curve obtained using an IgG panreactive monoclonal antibody (clone 8a4) with dilutions of a high positive reference serum which was assigned 10 000 arbitrary units/ml (AU/ml) when undiluted.[18]

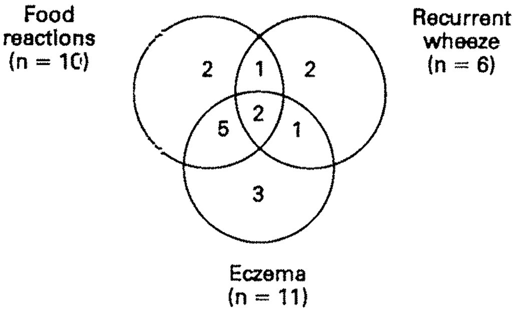

Figure 1 Categorisation of the 16 atopic children by evidence of atopic disease

STATISTICAL ANALYSIS

Even after log transformation *D pteronyssinus* IgG$_1$ antibody concentrations were not normally distributed at every age. However the log ratios of the concentrations at successive ages in each child did have normal distributions. Changes in *D pteronyssinus* IgG$_1$ concentrations between two ages were therefore given as the geometric mean ratio of the concentrations at the two ages with a 95% confidence interval. The corresponding one sample *t* tests gave the probability of the observed means if the true mean log ratio was zero (that is, if the ratio was 1); $p<0{\cdot}0125$ was taken as the level of significance to allow for multiple comparisons (Bonferroni method). The Mann-Whitney test was used to analyse differences within age groups. The probability level for a significant difference was adjusted to $p<0{\cdot}01$ to allow for five comparisons. Finally a sample size of 31 was theoretically able to have an 80% chance of detecting a significant difference at the 1% level of about 1·2 times the value of a SD. Bearing in mind that any SDs would be tentatively derived from actual study data with a less than perfect distribution, this meant that one might expect to detect differences down to 40–70 AU/ml, except at 7 days when variability was greatest.

Results

Every child had detectable concentrations of IgG$_1$ antibody to *D pteronyssinus* at all ages (fig 2). Concentrations were highest at 7 days, reached a nadir at 3 months, rose progressively up to 12 months but declined at 24 months. The 95% confidence intervals for the geometric mean ratio of concentrations at consecutive ages was calculated. One could be 95% sure that on average 12 month concentrations were between

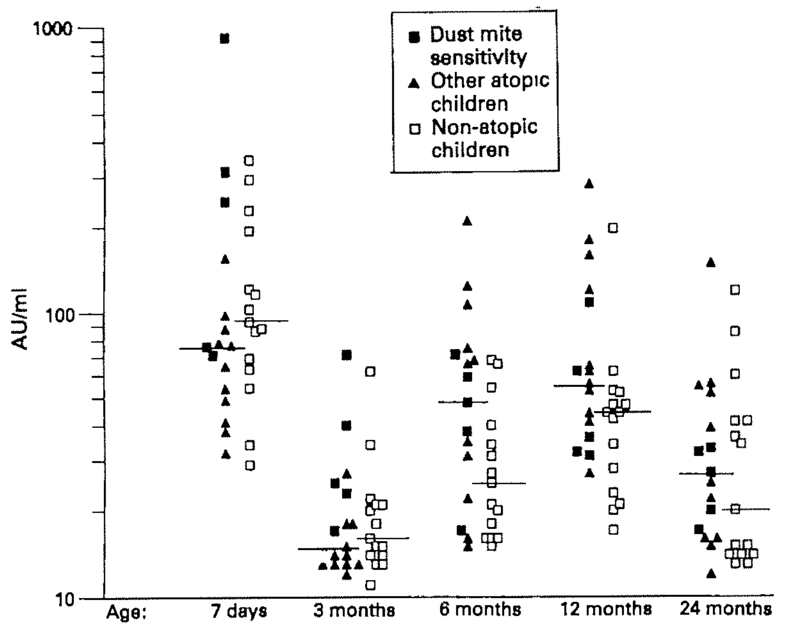

Figure 2 Concentrations of IgG_1 antibody to D pteronyssinus in five atopic children with dust mite sensitivity, 11 other atopic children, and 15 non-atopic children during the first two years of life. Median concentrations in the atopic and non-atopic subgroups at each age are indicated by the horizontal bars.

1·43 to 2·40 times higher than concentrations at 24 months, with 1·86 times as the best estimate (table 1).

Atopic children tended to have higher *D pteronyssinus* IgG_1 concentrations than non-atopic counterparts at 6 and 12 months, with $0·01<p<0·05$ (table 2). A trend for higher concentrations in the five dust mite sensitive individuals compared with the other 26 children was only seen at 3 months, with $p=0·03$ (fig 2). The six children who had recurrent wheezing had no tendency towards having higher values at any age.

IgG_4 antibody to *D pteronyssinus* was only found in 7 day sera and then in only three children. All three had mothers who had given florid skin reactions to *D pteronyssinus* with weals of 6 mm, 8 mm, and 11 mm in diameter respectively.

Table 1 Ratio of D pteronyssinus IgG1 antibody concentrations between successive age groups

D pteronyssinus IgG_1 concentration ratio	*Geometric mean ratio*	*95% Confidence interval*	*p Value*[*]
7 day.3 months	5 15	4 27 to 6 21	<0 0001
3 months:6 months	0 50	0·38 to 0 69	0 0001
6 months 12 months	0 70	0 56 to 0 89	0 0040
12 months.24 months	1·86	1 43 to 2 40	<0 0001

[*]One sample *t* test

Table 2 Comparison of median (range) D pteronyssinus IgG_1 antibody concentrations between atopic and non-atopic children

Age	*D pteronyssinus IgG_1 antibody concentration (AU/ml)*		*p Value*[*]
	Atopic children (n=16)	*Non-atopic children (n=15)*	
7 day	76 5 (32–914)	93 (29–344)	0 45
3 months	16 (12–71)	16 (11–62)	0 87
6 months	53 5 (15–210)	25 (15–68)	0·03
12 months	59 (27–283)	44 (17–197)	0 04
24 months	26 (12–149)	20 (13–119)	0 54

[*]Mann-Whitney test

Discussion

The validity of this study depends on the specificity of the assay for IgG subclass antibodies to *D pteronyssinus*. IgG_1 antibody binding to *D pteronyssinus* could be substantially inhibited by preincubation of the children's sera with the *D pteronyssinus* extract and cross reactivity with a different antigen (ovalbumin) was minimal. This implied the antibodies had reasonable affinity and specificity. The assay was therefore regarded to measure genuine *D pteronyssinus* IgG_1 antibodies in the children's sera.

The pattern of change in *D pteronyssinus* IgG_1 concentrations parallels changes in total IgG up to one year. The fall in concentrations at 24 months, however, suggests a specific immune response. A possible explanation for the fall is a reduction in the time spent maximally exposed to the antigen, as actual mite counts are unlikely to have altered drastically in every child's environment between the first and second years. Alternatively it could imply a switch in the subclass of IgG after prolonged exposure. IgG_4 would be the obvious alternative subclass[19] but no IgG4 antibodies to *D pteronyssinus* were detected in any child at 24 months.

Measurements made at 3 months and before reflect maternal rather than the infants' own antibodies. Rises in specific IgG_1 do occur between 7 days and 3 months, such as in IgG_1 to casein,[20] indicating an infant response at this time. A similar response to the dust mite may be obscured by relatively high concentrations of maternal mite specific antibody in these children. By 6 months, and certainly by 12 months, most maternal antibody will have cleared. Measurements at these times are therefore a better indicator of the infant response. It may be that responsiveness to the dust mite is greatest in infancy and begins to wane thereafter.

IgG_4 antibodies to *D pteronyssinus* had been undetectable at all time points during the first year in the study of 'unselected' children.[10] The present findings were similar. *D pteronyssinus* IgG_4 was only found in 7 day sera and every child with detectable concentrations had a mother who was allergic to the dust mite, reflecting the higher concentrations that might be expected in such mothers.[21] These antibodies may take longer to appear. They are certainly not present in all adults.[21]

Prospective documentation of atopic manifestations in the large cohort of children allowed the present study to focus on the most obviously atopic and non-atopic individuals in an attempt to clarify possible differences in the response to the house dust mite.

Although the differences in *D pteronyssinus* IgG_1 concentrations between atopic and non-atopic children at 6 and 12 months gave $0·01<p<0·05$, the statistical significance of these concentrations was interpreted cautiously in the light of multiple comparisons. The power calculation, however, indicated that significant differences smaller than 40–70 AU/ml might not be picked up by a study of the present size. Secondly the measurements were analysed according to atopic status as a means of grouping the children into those who were most likely and least likely to develop asthma. Differences in the *D pteronyssinus* antibody response may have been more apparent had it been possible to identify the future asthmatic children with greater precision.

It has been suggested that aeroallergen exposure in early infancy may represent a critical time in determining subsequent sensitisation and disease manifestation.[22] The present data intimates that *D pteronyssinus* IgG_1 antibody responses may be maximal during infancy. The highest IgG_1 responses at 6 months and thereafter were not, however, seen in those who developed IgE sensitisation to the dust mite (fig 2). Dust mite sensitivity was based on data from the first two years of life. Out of 30 children in the cohort followed up to two years, only six had given positive skin prick tests to *D pteronyssinus* of which five were in the present study. Clearly, many more of the children are likely to develop dust mite sensitivity when they are older.

This study demonstrates that IgG antibody responses to *D pteronyssinus* during the first two years in children predisposed to atopic disease are predominantly in the IgG_1 subclass. Higher *D pteronyssinus* IgG_1 concentrations at one year than at two years may reflect greater exposure or responsiveness. Finally the tendency for higher *D pteronyssinus* IgG_1 concentrations at 6 and 12 months in children with atopic manifestation in the first two years may become more clear cut in later years when analyses are made according to the presence of asthma.

We would like to thank the children and their parents for participation in the study, Miss Maria Sorooshian for help with the total serum IgE measurements, Miss Fiona Reid for statistical advice, and the National Asthma Campaign, Children Nationwide, and the Wellcome Trust for generous support.

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Archives of Disease in Childhood 1992; 67: 1027–1029

Breast feeding and oral rehydration at home during diarrhoea to prevent dehydration

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Abstract

In a case-control study we evaluated the role of maternal behaviour, as reflected in maintenance of breast feeding and the use of oral rehydration therapy (ORT) at home during acute diarrhoea, in preventing dehydration in infants and young children. A systematic 5% sample was taken of all children aged 1–35 months attending the treatment centre of the International Centre for Diarrhoeal Disease Research, Bangladesh, with acute watery diarrhoea of six days or less between August 1988 and September 1989. There were 285 children with moderate or severe dehydration as cases and 728 with no dehydration as controls in the study.

In a multivariate analysis using a logistic regression model we showed that withdrawal of breast feeding during diarrhoea was associated with a five times higher risk of dehydration compared with continuation of breast feeding during diarrhoea at home. Lack of ORT with either complete formula or a salt and sugar solution at home was associated with 57% higher risk of dehydration compared with receipt of a reasonable amount of ORT after controlling for several confounders. The confounding variables—that is, lack of maternal education, history of vomiting, high stool frequency, young age and infection with *Vibrio cholerae* 01—were also shown to be risk factors of dehydration. Health education programmes should promote continued breast feeding and adequate oral rehydration therapy for infants with acute diarrhoea at home.

(*Arch Dis Child* 1992;67:1027–1029)

For the home management of infants and children with diarrhoea, mothers with breast fed children are advised to provide oral rehydration therapy (ORT) and continue breast feeding during an acute attack of illness.[1] It is expected that this practice will help to protect the breast fed infant from developing a more severe illness. In this paper we assess the role of cessation of breast feeding and lack of ORT during diarrhoea, in the home management of acute watery diarrhoea in infants and children, in increasing the risk of dehydration.

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Accepted 4 April 1992

Patients and methods

PATIENT GROUPS

The study was conducted in the Clinical Research Centre of International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B) located in Dhaka, the capital city. The study population consisted of children aged between 1 and 35 months, presenting with watery diarrhoea for six days or less and evaluated clinically as 'cases', having moderate to severe dehydration, or as 'controls' with no signs of dehydration. A 5% systematic sample was drawn from all children meeting these criteria seeking care at ICDDR, B during the period of study, August 1988 to September 1989. The case-control design required a sample size of 200 in each study group (with $\alpha=0{\cdot}05$, power of 90%, and odds ratio of 2)[2]. Only children who had been receiving breast feeding up to the time of onset of diarrhoea were included in the study. Finally, 285 cases and 728 controls were entered in the study.

QUESTIONNAIRE ADMINISTRATION

Informed consent was obtained from mothers of all patients. We used a field tested, structured, interviewer administered questionnaire. Information was obtained from a clinical examination of each child, from carefully standardised anthropometric measurements, and from a general questionnaire on socioeconomic and demographic characteristics, medical history, and fluid and feeding interventions at home. We assessed dehydration according to simple clinical criteria set to minimise misclassification: none to mild (no clear signs of dehydration, with or without thirst); and moderate to severe dehydration with definite decreased skin elasticity and one or more of four signs—sunken eyes, failure to urinate for six hours, sunken anterior fontanelle, and rapid and weak pulse. Any child who had received any amount of breast milk during this episode of diarrhoea at home was considered to be breast fed. Mothers were asked about use of ORT at home (that is, use of prepackaged complete ORT formula or incomplete salt and sugar solution). The volume of ORT consumed was estimated from comparison with standard containers and expressed in millilitres.

The same questionnaire was given to the study group and to controls. Trained women interviewers interviewed each mother at her child's bedside and the interviewers were monitored for accuracy and completeness of the data. Interviewers had no prior knowledge of the purpose of the study nor were they aware of the classification of children as study cases or controls.

DATA ANALYSIS

We coded data collected by interview and physical examination. Data forms were visually checked for errors as they were collected and transferred to a microcomputer. We validated all data by a series of logical and range checks. Crude odds ratios were computed initially for the association of each factor of interest with dehydration (for example, withdrawal of breast feeding during diarrhoea and amount of ORT consumed at home). Then confounding variables were examined: each crude odds ratio was re-evaluated by controlling for each potential confounding variable one at a time by stratified Mantel-Haenszel summary statistics procedure.[3] [4] Evidence of confounding was examined by comparing the summary estimates of the odds ratio obtained from the stratified analyses with the crude estimates; if the estimate was appreciably altered then the variable was a confounder. The final step of analysis included logistic regression. The approach of modelling was structured. First a basic model was fitted including the variables of interest. Confounders identified from the stratified analyses were then entered into the model individually. Adjusted odds ratios (OR) and 95% confidence intervals (CI) of variables of interest were estimated while controlling for a number of confounders simultaneously, with state of dehydration as the dependent variable.[5]

Table 1 Comparison of cases and controls according to variables of interest and their confounders: univariate analysis

Variables	*No (%) cases (n=285)*	*No (%) controls (n=728)*	*OR (95% CI)*	*p Value**
Variables of interest				
Withdrawal of breast feeding during diarrhoea at home				
Yes	6 (2·1)	4 (0·5)	3·89 (0·96 to 15·84)	0·0576
No	279 (97·9)	724 (99·5)	1·00	
Total volume of ORT before admission (ml)†				
None	73 (25·6)	153 (21·0)	1·34 (0·93 to 1·92)	0·2523
≤250	85 (29·8)	219 (30·1)	1·09 (0·74 to 1·60)	
≥251	127 (44·6)	356 (48·9)	1·00	
Confounding variables				
Maternal education (years of schooling)				
None	175 (61·4)	351 (48·2)	1·71 (1·29 to 2·27)	0·0002
1+	110 (38·6)	377 (51·8)	1·00	
History of vomiting				
Yes	253 (88·8)	569 (78·2)	2·21 (1·47 to 3·33)	0·0001
No	32 (11·2)	159 (21·8)	1·00	
Maximum stool frequency in a 24 hour period				
≥11	127 (44·6)	254 (34·9)	1·50 (1·13 to 2·00)	0·0053
≤10	158 (55·4)	474 (65·1)	1·00	
Age of the child (months)†				
1–9	172 (60·4)	338 (46·4)	1·76 (1·32 to 2·33)	0·0001
10–35	113 (39·6)	390 (53·6)	1·00	
Cholera				
Isolated	29 (10·2)	19 (2·6)	4·23 (2·38 to 7·50)	<0·00005
Not isolated	256 (89·8)	709 (97·4)	1·00	

*χ^2 test.

†Those who had some ORT at home were divided into those who received median volume or less and those who received above the median volume. Age groups were categorised into median age or less and greater than median age.

Table 2 Factors (OR and 95% CI) associated with the presence of dehydration (dependent variable) in children with acute diarrhoea: multivariate analysis using logistic regression model

Variables	*Regression coefficient*	*SE*	*Adjusted OR (95% CI)*	*p Value*
Variables of interest				
Withdrawal of breast feeding during diarrhoea at home	1·654	0·684	5·23 (1·37 to 19·99)	0·016
ORT at home				
None	0·4505	0·192	1·57 (1·08 to 2·29)	0·019
≤250 ml	0·1657	0·175	1·18 (0·84 to 1·66)	0·343
Confounding variables				
Illiterate mother	0·4630	0·150	1·59 (1·18 to 2·13)	0·002
History of vomiting	0·7177	0·217	2·05 (1·34 to 3·14)	<0·001
High stool frequency in any 24 hour period (11+)	0·3774	0·156	1·46 (1·07 to 1·98)	0·015
Young age (1–9 months)	0·5929	0·152	1·81 (1·34 to 2·44)	<0·001
Cholera (positive)	1·648	0·321	5·20 (2·77 to 9·75)	<0·001

Results

The data from the two study groups are shown in table 1. Withdrawal of breast feeding—a rare event in both groups—was more common in cases than in controls (p=0·0576). Absence of ORT at home was more common among cases but did not reach statistical significance. Mothers of the children in the study group were more illiterate than those of controls (p=0·0002). A history of vomiting (p=0·0001) and high frequency of stool (p=0·0053) were more frequently reported by the study group than controls. Children among the cases were younger than the controls (p=0·0001). Cholera was more common among the cases than controls (p=<0·00005).

Table 2 shows the results of multivariate analyses by logistic regression. The adjusted OR and 95% CI of each variable of interest were computed. The mother's behaviour in withdrawing breast feeding during the infant's diarrhoea was associated with five times higher risk of dehydration compared with continuation of breast feeding during diarrhoea at home (OR=5·23, 95% CI=1·37 to 19·99, p=0·016); lack of ORT at home was associated with 57% higher risk of dehydration (OR=1·57, 95% CI=1·08 to 2·29, p=0·019) compared with receiving good amount of ORT after controlling for lack of maternal education (none *v* 1+ years of schooling), history of vomiting, high stool frequency (11+ in any 24 hours), young age, and infection with *Vibrio cholerae* 01. It should be noted that, although the odds ratio is large for cessation of breast feeding, the attributable risk for this community is small, because cessation of breast feeding during diarrhoea is rare. However, the population attributable risk for no use of ORT is substantial. The confounding variables adjusted for were also significantly associated with dehydration.

Discussion

The widely recommended practice of continued breast feeding during diarrhoea provides much needed nutrition to a breast fed child. Breast milk should also provide extra fluid during diarrhoea which may assist in preventing dehydration. The present study provides evidence, probably for the first time, that cessation of breast feeding during diarrhoea at home is an added risk for development of dehydration in breast fed children. This is plausible because, when breast feeding is continued during diarrhoea, the amount of breast milk intake is not much reduced.[6] Breast milk provides free water because of its low osmotic property; it has also been shown that continued breast feeding during diarrhoea reduces diarrhoeal frequency, duration, and ORT requirement.[7] In healthy, exclusively breast fed, infants breast milk has been shown to provide enough free water even in a hot environment.[8] It is, therefore, plausible that continued breast feeding during diarrhoea may protect a child from dehydration.

Is the cessation of breast feeding the mother's decision or the child's inability to feed? It may be a consequence of severe diarrhoea which is associated with dehydration. In the multivariate analysis, the OR for cessation of breast feeding has been adjusted for indicators of severity of dehydration like high stool frequency and for the presence of cholera and vomiting. In addition, the strength of the association would also suggest a cause and effect relationship. Cessation of breast feeding during diarrhoea was an uncommon event among this population. This cannot therefore, be a major contributor to the development of dehydration among infants and children in Bangladesh. In a study of rural Bangladesh, withdrawal of breast feeding was shown to be associated with severe disease, defined as a patient having altered consciousness or high fever or with severe dehydration, or resulting in death in hospital or after discharge.[9]

The usefulness of ORT in correcting dehydration once it has developed has been extensively documented.[1] It is also believed that early use of ORT may prevent dehydration. Surprisingly little evidence has been provided in the literature to support this belief. Our study provides evidence that home use of a convincing amount of ORT reduces the risk of dehydration by about 39%, although the amount of ORT fluid used at home may not have been adequate. The perceived severity of diarrhoea may lead to increased use of ORT at home by knowledgeable mothers and, therefore, the degree of protection demonstrated is likely to be an underestimate. In the multivariate analysis the OR was adjusted for indicators of severity such as high stool frequency and cholera. The presence of vomiting may alter ORT behaviour at home, so adjustment has also been made for this.

In interpreting the results of this study there are potential sources of bias that should be considered. To avoid misclassification, dehydration was so defined that only the children with unequivocal signs of dehydration were included as cases. Severely malnourished children could have been misdiagnosed as cases; this should occur no differently for those who received ORT or were breast fed at home. Furthermore, through the careful training of physicians involved in the study and the systematic evaluation of the accuracy of our data, misclassification of dehydration status was avoided. Selection of controls from the same reporting area as the study group should have minimised selection bias. Neither the mothers nor the interviewers were aware of the group status of any child during the study. The interviewers were not informed of the hypothesis being tested. The name of ICDDR, B and quality care provided free of charge for decades, together with lack of a comparable health facility in the area, minimised referral bias.

The results of our study have implications for the treatment of diarrhoea in the home. Although breast feeding is usually maintained during diarrhoea in Bangladesh, the consumption of other foods is often reduced.[10] In areas where either ORT is not given in adequate amounts or the practice of withdrawal of breast feeding during diarrhoea is common, a number of severe or fatal cases can be anticipated. In a nationwide study in rural India,[11] among 3590 mothers who were breast feeding their children at the time of the last episode of diarrhoea, 17% of the mothers stated that breast feeding should be stopped during diarrhoea; interestingly only 1% of them actually stopped breast feeding during the diarrhoeal episode. An analysis of respondents who believed that breast feeding should be stopped during diarrhoea revealed that literate mothers formed a significantly higher proportion holding attitudes that breast feeding should stop compared with illiterate mothers (25% *v* 17%). In some areas of India as many as 58% of mothers stated that breast feeding should be stopped during diarrhoea in a child.

Our data suggest a need for cost effective health education programmes to promote continued breast feeding and adequate ORT for infants with acute diarrhoea at home. Such programmes directed to mothers in the community should minimise the risk of severe dehydration in these patients.

This research was supported by the World Health Organisation and the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B) The ICDDR, B is supported by countries and agencies which share its concern for the health problems of developing countries. Current donors include the aid agencies of the Governments of Australia, Bangladesh, Belgium, Canada, Denmark, France, Japan, the Netherlands, Norway, Saudi Arabia, Sweden, Switzerland, the United Kingdom, and the United States; international organisations including the United Nations Development Programme, the United Nations Children's Fund, and the World Health Organisation, and private foundations including the Ford Foundation and the Sasakawa Foundation

We would like to thank Dr J R Hamilton, McGill University, Montreal for reviewing the paper We acknowledge the assistance of Mr Simon Cousens of the London School of Hygiene and Tropical Medicine in data analysis. We thank the clinicians of the ICDDR, B's Clinical Research Centre for their valuable support in the clinical assessment and care of the patients. We acknowledge Mr M A Khan and other interviewers for their excellent team work in data collection

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Archives of Disease in Childhood 1992; 67: 1030–1032

Reversible cerebral shrinkage in kwashiorkor: an MRI study

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Abstract

Protein energy malnutrition is associated with cerebral atrophy which may be detrimental to intellectual development. The aim of this study was to document the anatomical abnormalities which lead to the appearance of cerebral atrophy using magnetic resonance imaging (MRI) in the acute stage of kwashiorkor and to monitor changes during nutritional rehabilitation.

Twelve children aged 6 to 37 months requiring admission to hospital for the treatment of kwashiorkor were studied. The children were evaluated clinically, biochemically, and by MRI of their brains on admission and 30 and 90 days later. Brain shrinkage was present in every child on admission. White and grey matter appeared equally affected and the myelination was normal for age. At 90 days, the cerebral changes had resolved in nine and improved substantially in the remainder, by which time serum proteins and weight for age were within the normal range. The findings of this study suggest that brain shrinkage associated with kwashiorkor reverses rapidly with nutritional rehabilitation.

(*Arch Dis Child* 1992;67:1030–1032)

Protein energy malnutrition is an important nutritional deficiency world wide. In the last 40 years there has been significant progress in treating the acute effects of nutritional diseases, but the consequence of severe protein energy malnutrition on the developing brain is still ill defined.[1] A World Health Organisation (WHO) symposium concluded that despite the widely held opinion that malnutrition in early life jeopardises long term mental development, the evidence to support this opinion, especially evidence in man, is scanty.[2]

Stoch and Smythe followed up marasmic children for 15 years from infancy to investigate the effect of food deprivation on intellectual development.[3 4] They concluded that intellectual performance was impaired in the undernourished group when compared with controls. As the control children came from relatively stable home conditions, environmental factors may have accounted for the difference in outcome between the groups. Winick has stressed that undernutrition does not occur in isolation, but is part of a complex mixture of risk factors of genetic and environmental origin affecting subsequent development.[5] To overcome the environmental differences, Bowie *et al* used normally nourished siblings of the affected children as controls.[6] These siblings had grown up under the same environmental circumstances as the study subjects. In a prospective 15 year follow up of children with kwashiorkor no differences in educational achievement were noted between the study subjects and their siblings.

The affective changes which are a hallmark of the acute phase of kwashiorkor are accompanied by structural changes in the brain. Househam and de Villiers reported cerebral atrophy in 12 children using computed tomography.[7] Subsequently Househam found that the atrophy had resolved on scans performed an average of 14 months later.[8] He concluded that atrophy was apparent and suggested that 'cerebral shrinkage' more aptly describes the abnormalities.

The aim of this study was to document and define the anatomical abnormalities in the brains of children with kwashiorkor using magnetic resonance imaging (MRI). As MRI is safe and non-invasive, repeat scans could be performed 30 and 90 days later to monitor the sequence of changes during nutritional rehabilitation.

Patients and methods

Twelve children admitted to hospital for the treatment of kwashiorkor were studied; there were nine boys and three girls with a median age of 14·5 months (range 6–37 months). The diagnosis conformed to the criteria of the Wellcome classification of infantile malnutrition.[9] Children with a history of convulsions or previous disease involving the central nervous system were excluded.

We assessed the children to have mild, moderate, or severe disease on the basis of their clinical findings. Thus, children with mild disease had hair changes (straightening and lightening), dry skins, minimal pitting oedema, hepatomegaly of less than 3 cm below the costal margin, and no superadded infections. Children with moderate disease had dry generalised skin changes and nappy rash, hair changes, moderate pitting oedema, hepatomegaly greater than 3 cm below the costal margin, and superadded infections. Children with severe disease had raw, weeping skin lesions, hair changes, marked pitting oedema with swollen palms and soles, hepatomegaly greater than 3 cm below the costal margin, and superadded infections (for example, diarrhoeal disease, pneumonia, otitis media).

On admission to hospital, the weight, height, and head circumference of each child was documented and a blood sample was taken for

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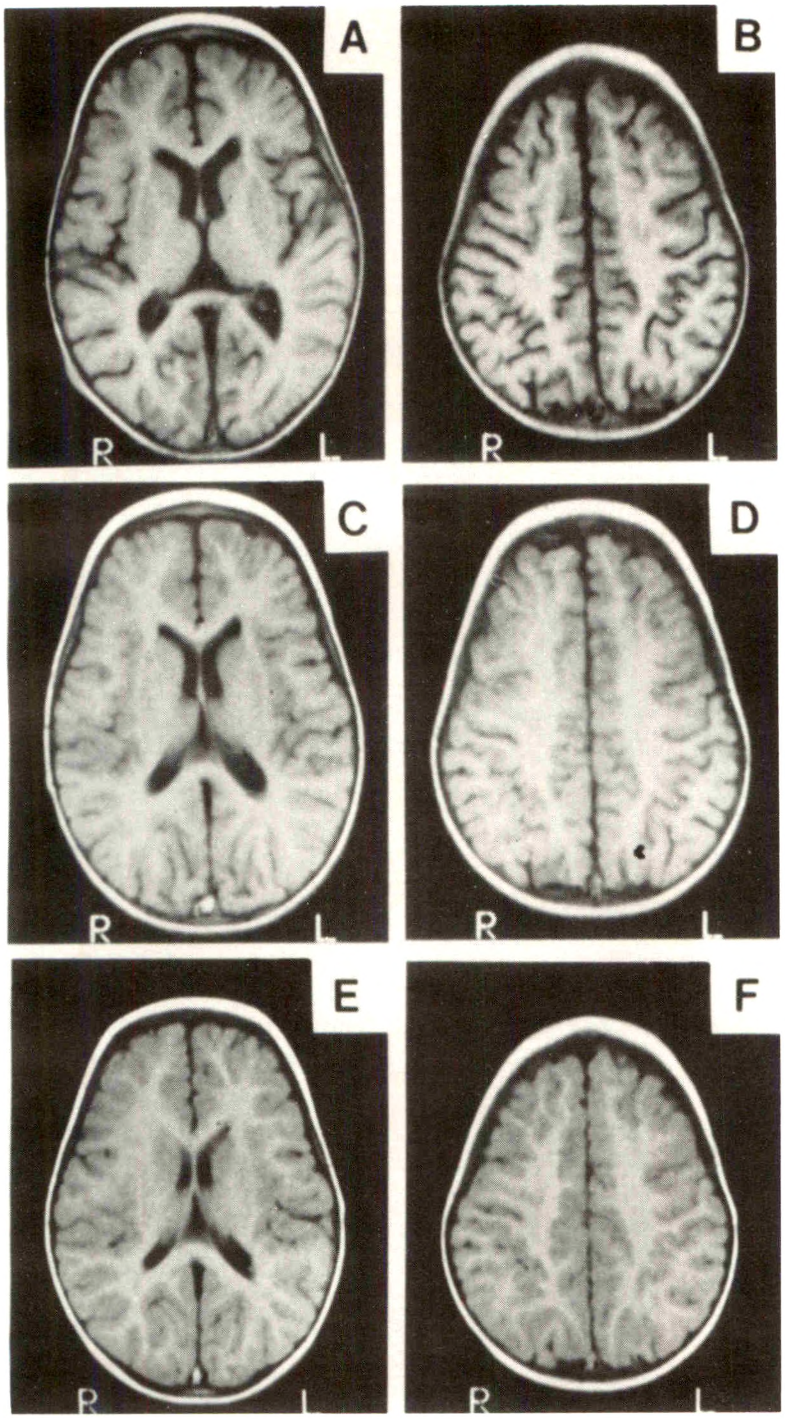
Accepted 19 March 1992

estimation of serum proteins and any other investigations necessary for the clinical care of the child. MRI of the brain was carried out within five days of admission. The clinical and biochemical measurements and MRI scans were repeated 30 and 90 days later.

Table 1 Weight, head circumference, and serum proteins on admission and during recovery. Figures are mean (SD)

	Admission	*Day 30*	*Day 90*
Weight (kg)	8·44 (1·82)	9·35 (2·08)	10·40 (1·82)
Expected weight (%)	75·6 (9·22)	81·4 (9·55)	95·4 (8·78)
Head circumference (cm)	45·9 (1·89)	46·4 (2·25)	46·7 (1·80)
Total protein (g/l)	41·8 (4·77)	66·8 (9·83)	67·4 (6·33)
Albumin (g/l)	17·8 (3·4)	35·2 (6·9)	37·2 (3·3)



A and B illustrate the typical MRI changes of cerebral atrophy as seen on admission. C and D show the improvement by day 30. E and F are day 90 scans, illustrating the rapid resolution of the signs of cerebral atrophy with refeeding (patient 4). A, C, and E are mid and B, D, and F are high axial views of the brain.

Table 2 Distribution of patients according to the degree of cerebral atrophy as assessed by MRI over time

Extent of cerebral atrophy	*No of patients*		
	Admission	*Day 30*	*Day 9*
Moderate	5	2	0
Mild to moderate	6	2	0
Mild	1	8	3

Infants were fed a commercial soya formula and a lactose free diet for the first 10 days. Additional folate, multivitamins, and trace metals were given. Iron was withheld during this period. Thereafter a mixed Western style diet containing cows' milk was gradually introduced. Patients received antibiotics according to laboratory and clinical indications. After discharge from hospital, supervised nutritional rehabilitation was continued in a convalescent facility.

Consent for the study was obtained from the escorting parent of each child before scans were performed. The study was approved by the ethics and research committee of the Medical Faculty of the University of Cape Town. No child requiring an MRI scan for a valid clinical indication was denied access by a child with kwashiorkor in whom the MRI scan was considered a research procedure.

Results

Of the 12 children studied, nine had moderate and three had severe disease. Head circumference was measured on admission in 11, and was within the normal range for 10 children. Six children had diarrhoea, one had pneumonia, and four had both. None of the children had meningitis or an infection of the central nervous system. There was an increase in weight and serum proteins over the 90 day period to within the normal range for age (table 1).

All the children had abnormal MRI scans of the brain. The abnomalities included widened cortical sulci (frontal, high parietal, sylvian fissures); widened interhemispheric fissure and cerebellar folia; enlarged ventricles (especially the frontal horns of lateral ventricles), and enlarged basal cisterns. The changes were compatible with 'cerebral atrophy' and were designated mild, mild to moderate, or moderate. In one child the changes were mild, in six they were mild to moderate, and in five they were moderate. By day 30, the majority of children showed an improvement in the degree of cerebral atrophy and by day 90 the changes had resolved in the majority (table 2). The figure shows the sequence of changes in a representative patient. Grey and white matter were equally affected and myelination appeared to be appropriate for age.[10]

There was no clear relationship between the clinical severity of the kwashiorkor or the serum albumin concentration on admission and the degree of cerebral shrinkage.

Discussion

MRI clearly demonstrated cerebral shrinkage in the acute stage of kwashiorkor in our patients.

Brain scans improved with refeeding and complete resolution occurred by 90 days in nine of the 12 patients. The underlying reason for the cerebral shrinkage is unclear and grey and white matter appeared equally affected.

In rats subjected to severe protein restriction, the lipid content of the brain has been shown to decrease.[11] Therefore, it may be postulated that loss of myelin lipid accounts for the cerebral shrinkage seen in our patients and it is feasible that restoration of lipid to the myelin membrane with refeeding accounts for the reversal of the cerebral shrinkage. However, in our study, the myelination was assessed as appropriate for age.

Improvement in brain size was apparent on day 30 of nutritional rehabilitation in the majority of patients. This rapid improvement suggests that the changes in size may relate predominantly to fluid shifts between various compartments and to a lesser degree to fat or protein abnormalities in the brain. Heinz *et al* have reported 'reversible cerebral atrophy' in patients with anorexia nervosa and propose that fluid shifts account for the phenomenon.[12] Fluid moves out of intravascular spaces as a result of decreased colloid osmotic pressure and floods the subarachnoid spaces, dilates the ventricles, and widens the cisternal spaces and sulci. When nutrition is improved the plasma proteins rise, the extracellular fluid moves back into the intravascular space.

Taken together with studies of intellectual function using carefully selected controls, our findings support the view that anatomical recovery is relatively rapid and that the child's ultimate intellectual status is the result of the interaction between a complex mixture of risk factors of genetic and environmental origin. If environmental factors and social stimulation at the time of undernutrition are favourable, the chances of retarded development and long term adverse effects are diminished.

As the environment plays a crucial part in determining the outcome of the developmental process, the rehabilitation of children with kwashiorkor must include in addition to adequate nutrition, stimulation to provide for intellectual and emotional growth.

This investigation was supported by the Bernard and Rita Brodie Associateship in Nutrition and the Research Insitute for Medical Biophysics of the South African Medical Research Council. We wisk to thank the staff of the paediatric wards for the day to day care of the children.

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Archives of Disease in Childhood 1992; **67**: 1033–1035

Reversible mitochondrial myopathy with cytochrome *c* oxidase deficiency

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Accepted 27 March 1992

Abstract

Two siblings, a boy and a girl born in a nonconsanguineous marriage, presented with a similar clinical course. Sucking and breathing difficulties appeared within a few weeks of birth. Clinical examination revealed profound muscular hypotonia, hepatomegaly, increased serum creatine kinase activities, and lactic acidosis. Both infants were treated with gavage feeding, the boy also needing ventilatory support. Clinically they improved gradually. Now, the boy aged 4 years and the girl aged 28 months are free of clinical signs. Muscle biopsy specimens taken at 3 months showed, in both, ragged red fibres, abnormal mitochondria, and reduced cytochrome *c* oxidase (COX) staining. Biochemical analysis showed COX activity to be reduced to about 25% of the normal mean. The second biopsy specimen from the boy at 16 months was normal on morphological examination, but the girl's second specimen at 13 months still showed abnormal features. These cases are examples of the rare benign reversible COX deficiency. Early diagnosis is crucial to provide intensive treatment until spontaneous clinical improvement appears.

(*Arch Dis Child* 1992;**67**:1033–1035)

Infantile myopathies with cytochrome *c* oxidase (COX) deficiency are rare conditions with both benign and fatal outcome.[1–3] The mode of inheritance and the mechanism of the reversibility are still unknown.

We describe a pair of siblings, who both show COX deficiency with a benign clinical course.

Case reports

CASE 1

The boy was the first child from a nonconsanguineous marriage. Both parents were healthy and the family history was unremarkable with no neurological disorders. The fetal movements were weak. The delivery was uncomplicated, and the Apgar score at 1 and 5 minutes was 5 and 8, respectively. The boy showed hyperbilirubinaemia, but was discharged at the normal time of 7 days. At home he developed sucking difficulties and lost weight. When readmitted to hospital at 3 weeks he was lethargic, dehydrated, and severely hypotonic. The liver was 5 cm below the costal margin and he had profound acidosis. After correction of the dehydration and acidosis, he improved temporarily, but at the age of 6 weeks his condition worsened again making artificial ventilation necessary for 14 weeks. Blood chemistry showed severe metabolic acidosis. Blood lactate concentration was 17·4 mmol/l (reference values <1·8 mmol/l). Serum creatine kinase activity was also considerably increased 1402 U/l (<220 U/l). Blood ammonia was slightly increased at 99 μmol/l (<50 μmol/l). Serum total carnitine was normal at 36·5 μmol/l (>35 μmol/l), but only 3% of it was in unesterified form. He received carnitine supplementation (100 mg/kg/day) from the age of 2 months. Gradually his condition started to improve. Abnormal blood lactate and serum creatine kinase values declined to near normal values during the first year of life, but periodic increases in creatine kinase were detected afterwards (fig 1). Muscular hypotonia showed slow but steady improvement. He learned to walk by 20 months and now at 4 years he can pedal a tricycle for several kilometres and shows no muscle weakness. His intellectual development has been normal. Carnitine supplementation was stopped at the age of 27 months.

CASE 2

The younger sister was admitted to hospital at 12 weeks for sucking difficulties, poor weight gain, and severe hypotonia. She also had increased blood lactate concentration at 16·8 mmol/l (fig 1) and serum creatine kinase activity at 798 U/l. Serum carnitine concentration was 36·0 μmol/l (7% unesterified). She received oral carnitine supplementation (100 mg/kg/day) from the age of 3 months until 18 months. She had gavage feeding for six months after hospitalisation, but no artificial ventilation. Her motor development was slightly delayed. At 18 months she was able to climb up from the sitting position and take a few steps without support, and now at 28 months her muscle strength is normal.

Investigations

MUSCLE BIOPSY

Surgical muscle biopsy specimens were taken with informed consent from the parents from vastus lateralis muscles at the age of 3 months. A second biopsy was carried out in case 1 at the age of 16 months and in case 2 at the age of 13 months.

MORPHOLOGICAL METHODS

Cryostat sections were stained with haematoxylin and eosin, periodic acid Schiff stain (PAS), reduced nicotinamide adenine dinucleotide (NADH) tetrazolium reductase, modified Gomori stain, as well as ATPase after preincubations at pH 10·4, 4·6, and 4·3. COX staining was carried out according to Dubowitz.[4] Samples

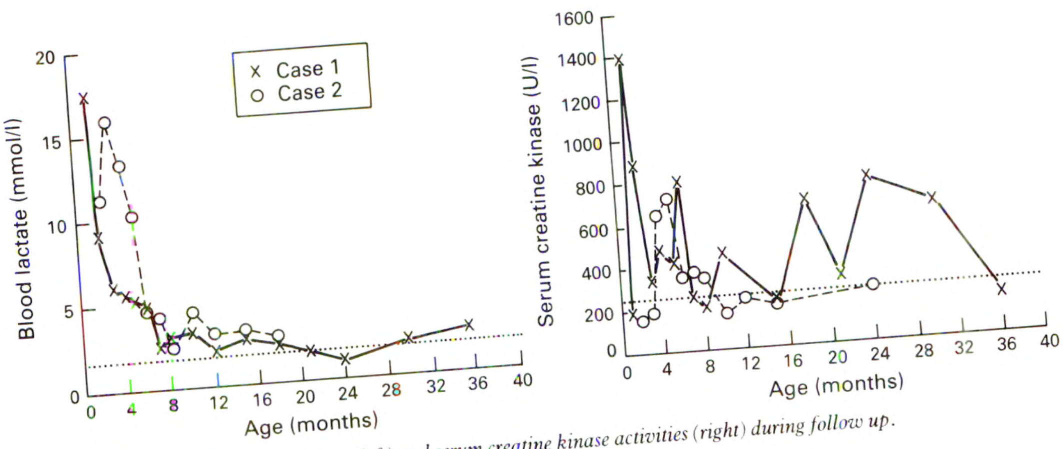

Figure 1 Blood lactate concentrations (left) and serum creatine kinase activities (right) during follow up.

for electron microscopy were processed according to standard technique.

BIOCHEMICAL ANALYSES

Portions of the first biopsy specimens of both cases were immediately frozen in liquid nitrogen and stored at −70°C until analysed. Biopsy specimens were then homogenised in nine volumes of 0·15 M potassium chloride with 50 mM Tris hydrogen chloride (pH 7·4) in all glass motor driven homogenisers. COX and other mitochondrial enzymes were measured in the supernatant fluid after centrifugation at 1000 *g* for 15 minutes by methods previously described.[3]

SKIN FIBROBLAST CULTURES

Fibroblasts were grown from a skin biopsy specimen taken from case 1 and cultured in Eagle's basal medium supplemented with 10% fetal calf serum. Enzyme activities of pyruvate carboxylase and pyruvate dehydrogenase were kindly measured by Dr E Holme (University of Gothenburg, Sweden) and those of long and medium chain fatty acid β-oxidation by Dr C Vianey-Liaud (Hospital Debrousse, Lyon, France).

Results

MORPHOLOGICAL FINDINGS

The first muscle biopsy specimen taken from case 1 at 3 months showed profound changes including necrotic fibres, increased ventilation of fibre size, split fibres, increased amount of internal nuclei, and fatty infiltration (fig 2A). Numerous ragged red fibres were shown with modified Gomori stain suggesting mitochondrial involvement. An electron micrograph from the same specimen showed swollen mitochondria containing tightly packed concentric cristae embedded in abundant glycogen matrix (fig 2B). Some of the mitochondria were remarkably increased in size. Histochemical COX staining of the same biopsy specimen

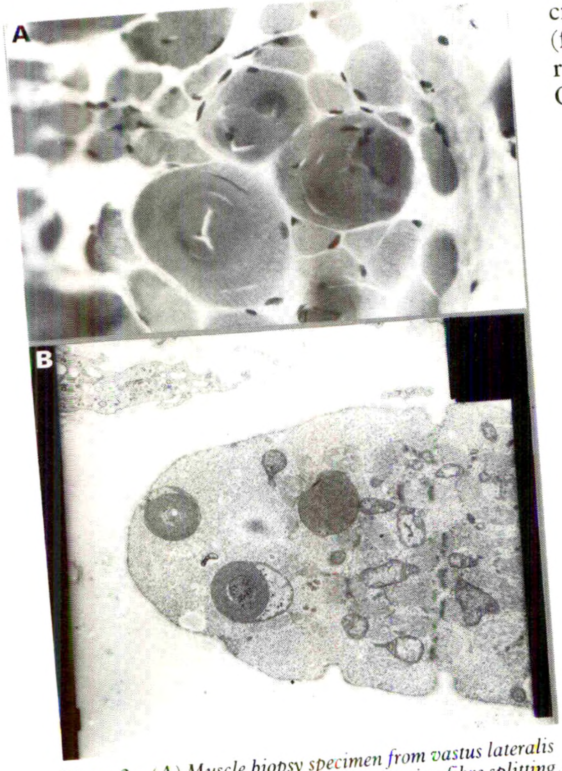

Figure 2 (A) Muscle biopsy specimen from vastus lateralis muscle (case 1) at the age of 3 months showing fibre splitting, a whorled fibre, fibre size variation, and internal nuclei. (Stained with haematoxylin and eosin, magnification×250.) (B) Electron micrograph from the same specimen showing swollen mitochondrial with tightly packed concentric cristae embedded in abundant glycogen matrix (magnification×18 000).

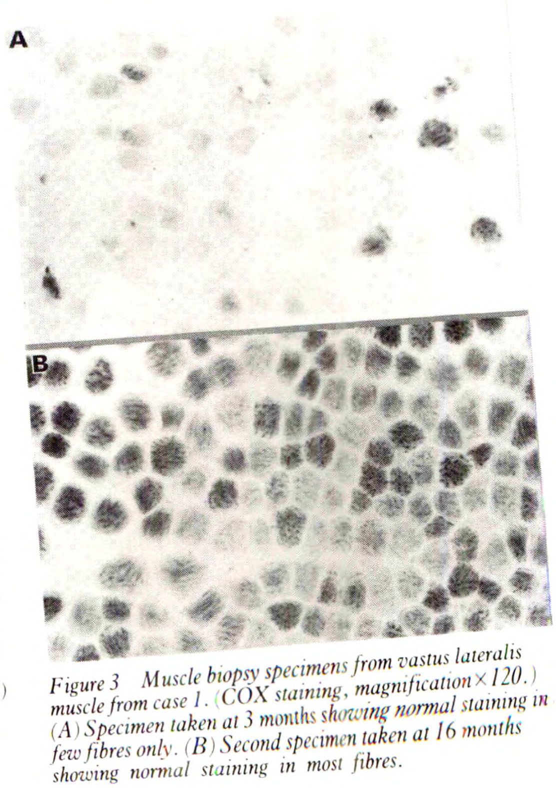

Figure 3 Muscle biopsy specimens from vastus lateralis muscle from case 1. (COX staining, magnification×120.) (A) Specimen taken at 3 months showing normal staining in few fibres only. (B) Second specimen taken at 16 months showing normal staining in most fibres.

Table 1 Mitochondrial enzyme analyses in muscle tissue biopsy specimens from the two cases and 38 control patients. (Activities are expressed as μmol of substrate used per min/g of tissue)

	Case 1 at 3 months	*Case 2 at 3 months*	*Controls Mean (SD)*
Cytochrome *c* oxidase	0·74	0·73	2·86 (0·53)
Succinate cytochrome *c* reductase	1·07	2·10	0·75 (0·20)
Rotenone sensitive NADH cytochrome *c* reductase	1·32	0·59	1·17 (0·47)
Citrate synthase	15·73	39·70	11·35 (2·4)
NADH dehydrogenase	59·85	8·71	35·21 (6·3)
Succinate dehydrogenase	1·07	3·40	1·68 (0·45)

Table 2 Clinical and biochemical findings in reversible COX deficiency

	DiMauro et al 1983[1]	*Zeviani et al 1987*[2]	*Own cases*	
Family history	–	–	Siblings	Siblings
Pregnancy and delivery	Normal	Normal	Normal	Normal
Onset of symptoms (weeks)	<2	<6	<3	<12
Weak cry	+	–	+	+
Sucking difficulties	+	+	+	+
Muscular hypotonia	+	+	+	+
Extraocular muscle weakness	–	+	–	–
Macroglossia	+	–	–	–
Hepatomegaly	+	+	+	–
Gavage feeding	+	+	+	+
Respiratory support	–	+	+	–
Blood lactate at onset (mmol/l)	28	12	18	16
COX activity at 1–4 months	6%	8%	25%	25%
Blood lactate at 11–14 months	3	Normal	3	3
COX activity at 11–18 months	nd	33%	nd	nd
Residual signs	Waddling gait (33 months)	Cannot walk (20 months)	None (4 years)	None (28 months)

nd= not determined.
Reference values for blood lactate are 0·70–1·80 mmol/l. COX activity refers to relative values as compared with controls

showed abnormal reaction in most fibres. Some fibres showed a faint reaction, whereas the majority remained completely non-reactive (fig 3A). In the second biopsy specimen taken at 16 months the general structure of the muscle was already normal. No ragged red fibres were observed and COX staining revealed a relatively homogenous reaction (fig 3B).

A muscle biopsy specimen from the case 2 at 3 months was identical to the first specimen from case 1, but her second specimen, taken at the age of 13 months, still showed abnormalities compatible with mitochondrial myopathy, including an uneven COX staining pattern.

BIOCHEMICAL FINDINGS

A consistent finding in the two biopsy specimens taken at age 3 months was the reduction of COX activity to about 25% of the controls (table 1). Pyruvate carboxylase and pyruvate dehydrogenase as well as fatty acid β-oxidation activities were normal in the fibroblast cultures obtained from case 1.

Discussion

Reversible mitochondrial myopathy in these two siblings bears close resemblance to two previous cases.[1 2] Although reversal of COX activity was not documented by enzyme analysis, it is clearly apparent from the COX staining in the successive biopsy specimens.

The four cases share several clinical characteristics in common (table 2). The first symptoms appear soon after birth. Muscle tissue is severely affected, transient hepatomegaly and macroglossia may appear, but the myocardium and central nervous system do not seem to be affected. Hospitalisation is needed, and in some cases ventilatory support also. The pace of recovery may vary, as seen in our two siblings, but clear improvement is usually detected within the first year of life. The low serum free carnitine concentration prompted us to start carnitine supplementation. Yet, because we had no measurement of its concentration in muscle, it is impossible to estimate if there was a true carnitine deficiency. Clinical improvement seems to be associated with a decline in blood lactate concentrations. The first described patient[1] had still a waddling gait at the age of 33 months, and the second patient[2] was unable to walk at the age of 20 months, causing some uncertainty about the reversibility of the syndrome. Our first patient has the longest follow up, and at the age of 4 years he has no muscle weakness at all. Our second patient is keeping up with her peers at the age of 2 years, suggesting that functional recovery may be complete in these cases. It should be noted, however, that our first patient showed periodic increases in serum creatine kinase activity, despite his normal muscle strength.

These are the first familial cases reported. The condition is likely to be inherited. Reversiblity of COX deficiency is a unique finding among inherited metabolic diseases, and it is not completely understood at the moment. The enzyme is composed of 13 subunits, three of which are encoded by mitochondrial DNA. There is also evidence of tissue specific isoforms.[5] All four cases manifested purely as a myopathy. As there is no evidence of mitochondrial transmission, a mutation in developmentally regulated nuclear encoded subunits seems a plausible explanation.

Reduced COX activity is associated with various clinical syndromes, some of them resembling Leigh's syndrome and affecting predominantly brain, some manifesting predominantly as a myopathy.[6] In clinical situations the differential diagnosis is mainly between the fatal and the benign reversible myopathy. It is possible that the use of monoclonal antibodies against COX subunits may bring a solution to the problem,[7] although more experience is needed to prove their diagnostic value. Until then, careful follow up with adequate life support is needed until the benign form can be differentiated from the fatal one.

This study was supported by National Academy of Medical Sciences, Arvo and Lea Ylppo Foundation

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Archives of Disease in Childhood 1992; 67: 1036–1037

Recurrent parotitis

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Abstract

Recurrent parotitis in children is a well described but rare condition of unknown cause. The clinical features of 11 children with recurrent parotitis are described.

(*Arch Dis Child* 1992;67:1036–1037)

The aetiology and pathogenesis of chronic recurrent parotitis in children has of yet not been satisfactorily explained. It is characterised by a recurrent, painful swelling of the parotid gland, often with purulent sialorrhoea.

In most cases, sialectasis has been documented, sometimes in combination with ductal changes.[1 2] The treatment should be conservative as the disease has a spontaneous recovery at puberty in most of the cases.[3] We report a follow up of 11 cases of chronic recurrent parotitis.

Patients and methods

During the years 1984–9, 11 cases of chronic recurrent parotitis in children was followed up at the paediatric ambulatory, day care department at Hasharon Hospital. The diagnosis was based on clinical criteria and in five patients also on the radiological demonstration of sialectasis.

Results

The clinical features of the 11 children with recurrent parotitis are described in the table. Boys were affected more than girls. The age range was between 1·2 and 7 years. The mean exacerbation rate per year was 4·9 with a range of two to 12 attacks per year. The duration of the attack was two to five days. In most exacerbation attacks a mucopurulent discharge was pressed from the parotid gland. Bacterial culture revealed *Streptococcus viridans* and *Haemophilus influenzae* in most of the cases.

The symptoms were unilateral in six patients (right side n=3, left side n=3) and bilateral in five patients. All patients received antibiotics orally as the only treatment for exacerbations. Because of frequent recurrences of infection with abscess formation, patient 6 underwent total parotidectomy with good results. There were no underlying systemic diseases like Sjögren's syndrome, cystic fibrosis, rheumatoid arthritis, or systemic lupus erythematosus. Serological studies did not show a recent infection of mumps, Epstein-Barr virus, cytomegalovirus, or enteroviruses at the first presentation.

Eight out of 11 patients were completely free of clinical symptoms for at least 1·5–2 years. Two patients had a decrease in exacerbation rate. Patient 5 had three attacks during the last 12 months and patient 11 had one attack during the last 18 months of follow up. The patient who underwent partotidectomy has been completely free of symptoms for at least 2·5 years.

Discussion

Recurrent parotitis in children is a rare disease. The age of onset has been reported to range from 8 months to 16 years[4] with the highest incidence between 3 to 6 years of age as documented in our patients.[5 6] More boys than girls were affected.[3 4] Different theories of aetiology and pathogenesis have been discussed over the years.

Bailey[7] and Smith[8] proposed a congenital abnormality as a predisposing factor. Familial background[1 6 9] and impaired rates of secretion was also reported.[10] Immunological factors may also be involved.[11 12]

The affected children had multiple episodes of swelling of one or both parotid glands, sometimes in combination with pain and fever. Sialography reveals sialectasis in most cases with ductal changes in about one third of the

Clinical features of 11 children with recurrent parotitis

Patient No	*Sex*	*Age of first presentation (years)*	*No of recurrences/year*	*Duration of symptoms (years)*	*Unilateral parotitis*	*Bilateral parotitis*	*Follow up period (years)*	*No of years symptom free*
1	M	2	5	3	+		5·5	3
2	F	5	4	4	+		5	1·5
3	F	6	4	2·5	+		4·5	2
4	F	7	2	3·5		+	5	2·5
5	M	1·2	12	3		+	3·5	Decrease*
6	M	5	6	2	+		4·5	2·5
7	F	4	4	3		+	4·5	1·5
8	M	5	5	2	+		4	2
9	M	5·5	4	4	+		5	2
10	M	5	5	3		+	4·5	1·5
11	M	3	3	5		+	5	Decrease*

*Decrease in the exacerbation rate during follow up period
+=Unilateral or bilateral parotitis present

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Accepted 6 May 1992

cases. The sialectatic changes are often found bilaterally, even if symptoms are unilateral. Normal sialograms have also been reported in symptomatic recurrent parotitis.[13 14]

No correlation between the extent of the sialographic changes and clinical findings can be found.[13] In most cases, the disease ends at puberty with a recurrence rate after puberty in 10–20% of the cases. Virgilio *et al* proposed the evidence of a clear distinction by clinical and development features between the infantile and adult form of chronic parotitis.[14] Mucopurulent saliva may be pressed from the parotid duct and it can be a sign of persistent low grade infection. In most attacks, in the patients included in our follow up, bacterial culture of the mucopurulent discharge revealed *S viridans* and *H influenzae*.

All patients received oral antibiotics as the only treatment for exacerbation. Eight of the 11 patients were completely free of clinical symptoms for at least 1·5–2 years. Two patients had a decrease in the exacerbation rate during the follow up period. The patient who had total parotidectomy was completely free of symptoms for 2·5 years. Because of the tendency of spontaneous recovery of the disease before late puberty, conservative treatment and follow up are recommended in most cases.

Surgical treatment, for example ligature of Stensen's duct,[10 15] parotid parasympathectomy and parotidectomy[16] are only recommended in the more severe cases. If parotidectomy is indicated then total parotidectomy is necessary with the associated substantial risk of post-operative facial weakness. The risk of permanent sequelae is small.[16]

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Archives of Disease in Childhood 1992; 67: 1038–1039

Solitary mastocytoma causing recurrent blistering in infancy

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Accepted 24 March 1992

(*Arch Dis Child* 1992;67:1038–1039)

Abstract

Two children with solitary mastocytoma in infancy, both of whom had recurrently blistering scalp lesions, are reported in order to emphasise the diagnostic importance of this distinctive history.

Cutaneous mastocytosis in infancy or childhood usually presents with multiple lesions but mastocytomas are solitary in about 10% of cases.[1] Isolated lesions may not be easy to diagnose on clinical appearances but nearly always have a history of recurrent blistering.[2–3] We report two typical cases of solitary mastocytoma in order to emphasise the importance of this history.

Case reports

CASE 1

An otherwise healthy girl born at term was noted at birth to have a scabbed occipital lesion attributed at the time to a scalp electrode. At 9 days an area adjacent to the scab became swollen and cystic; aspiration produced sterile serosanguinous fluid. The possibility of an occipital meningoencephalocele was considered but excluded by ultrasonography. In the next few weeks the lesion swelled intermittently on five further occasions (fig 1), each time subsiding over a few days during antibiotic treatment. When seen by one of us at 11 weeks the diagnosis of mastocytoma was considered, particularly as the quiescent lesion urticated when rubbed. There was no other evidence of mastocytosis. A small diagnostic biopsy was arranged. At the end of the procedure the surgeon noted that the child went transiently 'bright red from top to toe' without disturbance of vital signs. Histology confirmed mastocytoma (fig 2). Over subsequent months the lesion continued to urticate periodically, and the infant had several episodes of flushing and restlessness each lasting an hour, but unrelated to change in the lesions. By the age of 3 years, all these episodes had ceased, and the lesion had become simply an area of redness with some overlying hair loss.

CASE 2

An infant boy had a scalp lesion noted at birth which blistered on at least three subsequent occasions. The episodes were treated by aspiration and antibiotics by his general practitioner At the age of 6 months he was referred to a surgeon who suspected an infected sebaceous cyst and attempted excision of the lesion. Histology was that of a mastocytoma, and he was referred to us. When seen, the incompletely excised lesion consisted simply of redness and coarse scale. Two other 0·5 cm telangiectatic macules were present on right thigh and buttock, but none of the lesions urticated on rubbing. Despite the excision biopsy, the scalp lesion has continued to blister intermittently, but there has been no generalised flushing.

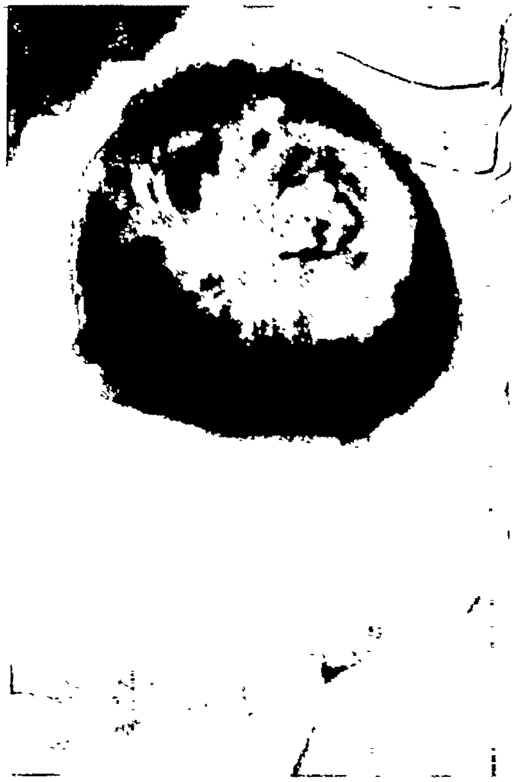

Figure 1 A photograph, taken by the parents, of the lesion during an episode of blistering.

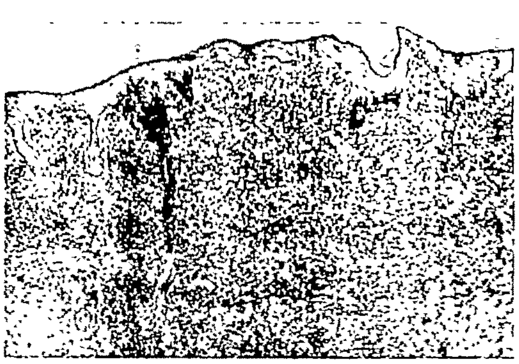

Figure 2 Histology showing mast cells densely packed within the upper dermis.

Discussion

We wish to draw attention to this disorder, because while relatively uncommon, the presentation is distinctive, and earlier recognition of our cases might have avoided some unnecessary investigation and treatment.

The commonest presentation of cutaneous mastocytosis in childhood is urticaria pigmentosa appearing as numerous small round or ovoid red or red-brown macules or papules, usually in the first six months to two years of life.[1] In most cases the lesions urticate on rubbing, due to mediator release (Darier's sign), but vesiculation or frank blistering is common in lesions in infancy.

A multiplicity of these nodular or blistering lesions suggests the diagnosis but our two cases suggest that diagnosis of mastocytomas which are solitary is less easy. However, 38 cases of solitary mastocytomas in four early series[1–4] indicate that the presentation is just as characteristic. Half the solitary lesions were present at birth, most by 3 months, and all but five by the age of 2 years. The usual site was on the trunk or limbs, but not palms or soles; in contrast with our cases, only two of 38 had head or neck lesions. Lesions were yellow, tan or red-brown in colour, slightly elevated or macular, and ovoid, 0·5 to 3 cm in largest diameter. On the basis of these appearances, the clinical differential diagnosis included melanocytic naevi, xanthomas, or juvenile xanthogranulomas. The diagnosis of solitary mastocytoma was suggested by a positive Darier's sign in only half the cases, but a history of blistering was recorded in 25 and probably more of the cases. Other cases have experienced episodic flushing.[5] The diagnosis can be confirmed by biopsy; unfortunately examination of the serosanguinous blister fluid is not useful as it usually contains neutrophils rather than mast cells. The course of solitary mastocytoma is benign; those lesions not cured by excision appear to improve or resolve during early childhood.[1, 3]

Blistering mastocytomas in the neonatal period or in infancy have initially been diagnosed as bullous impetigo or epidermolysis bullosa,[1] or even cigarette burns (Camille Lazarro, personal communication). It is therefore important for appropriate management to recognise that in infants a history of episodic blistering or swelling at a single site is almost pathognomonic of solitary mastocytoma.[2, 3]

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Pituitary gigantism

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Accepted 18 March 1992

(*Arch Dis Child* 1992,67:1039–41)

Abstract

A case of pituitary gigantism resulting from a pituitary adenoma which secreted growth hormone is described. The patient was successfully treated by surgery, which led to the normalisation of endogenous growth hormone secretion. An acceptable final height was achieved with high dose intramuscular testosterone treatment.

The management of pituitary gigantism is difficult and often requires multiple approaches including surgery, radiotherapy, and medical treatment. It has not been established whether surgery alone can normalise spontaneous growth hormone secretion, for there is the possiblity of an underlying abnormality in the secretion of growth hormone releasing hormone and somatostatin. We report our successful experience in the transsphenoidal removal of a pituitary adenoma and the restoration of normal growth hormone secretion in a boy with gigantism.

Case history

A 13 year old boy presented with a five year history of rapid growth. He was born at full term with a weight of 3200 g and length of 51 cm. He grew at a normal rate until 7 years of age when it was noticed he had large hands and required increasing shoe sizes. At the age of 10 years he was taller than a brother 14 months his senior. Immediately before referral he grew 20 cm over a 10 month period. There was no family history of tall stature (mother's height 163 cm, father's height 178 cm) and his four siblings were of average height.

On examination his height was 187·5 cm (height SD score +3·57) and his weight was 78 kg. He was in Tanner stage 4 puberty (testes 12 ml). His hands and feet were large with slight sweating. Mild prognathism was noticed. His bone age corresponded to a male standard of 13 years according to the Greulich-Pyle standard.[1] His predicted final height, calculated according to the method of Bailey-Pinneau,[1] was 214 cm.

A cranial computed tomogram demonstrated a pituitary fossa of normal size containing an intrasellar pituitary mass of 12 mm diameter (fig 1).

ENDOCRINE INVESTIGATIONS

Spontaneous nocturnal growth hormone secretion was assessed by taking blood samples at 20 minute intervals (8 pm to 8 am) using previously described methods.[2] There was persistent raised growth hormone concentration throughout the 12 hour sampling period with a mean 24·9 µg/l. Growth hormone concentration did not return to the baseline and no obvious episodic secretory pattern was documented (fig 2 shows that the number of pulses defined by PULSAR algorithm[2] was three). Insulin-like growth factor I (IGF-I) was significantly increased at 134 nmol/l (normal range 34–97 nmol/l). A four hour glucose tolerance test revealed normal carbohydrate tolerance but there was no suppression of growth hormone concentrations (growth hormone concentration ranged from 35–60 µg/l). No other hormonal abnormality of the anterior pituitary gland was observed.

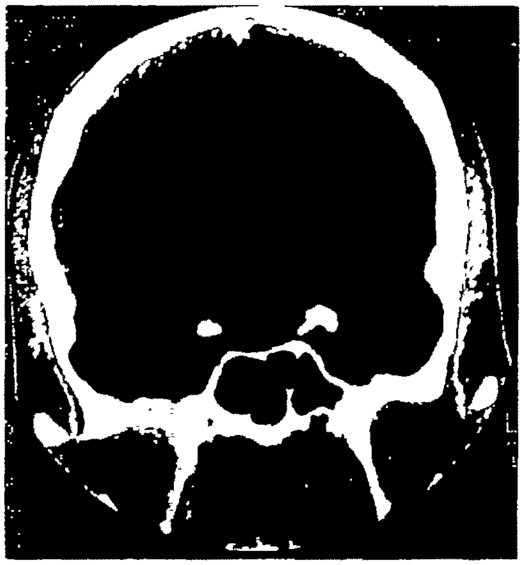

Figure 1 A computed tomogram performed before surgery showing a mass in the pituitary fossa which measured 12 mm in diameter

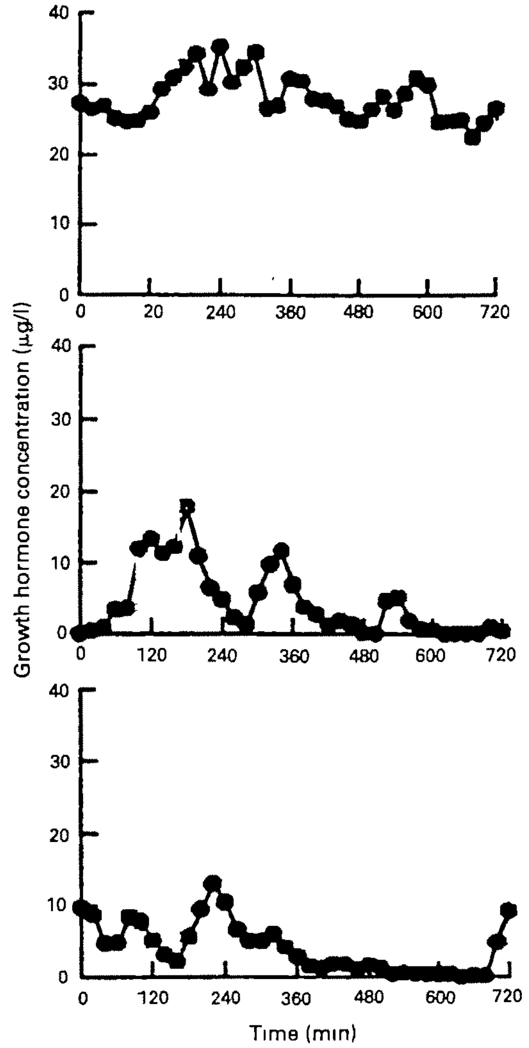

Figure 2 Nocturnal growth hormone secretory profiles assessed before surgery (upper panel), one month (middle panel), and 15 months (lower panel) after surgery

TRANSSPHENOIDAL ADENOMECTOMY

At surgery, a well defined mass in the pituitary fossa was removed by the transsphenoidal approach. No other pituitary tissue was disrupted. Histology revealed an eosinophilic adenoma.

POSTOPERATIVE PROGRESS

The patient recovered well from the operation without apparent endocrine disturbance. A 12 hour nocturnal growth hormone study was performed two months after the adenomectomy. The mean growth hormone had decreased to 4·4 µg/l and there was a normal growth hormone secretory pattern with interpulse values below the detectable limit (fig 2). IGF-I returned to normal (60·0 nmol/l). Further assessment of

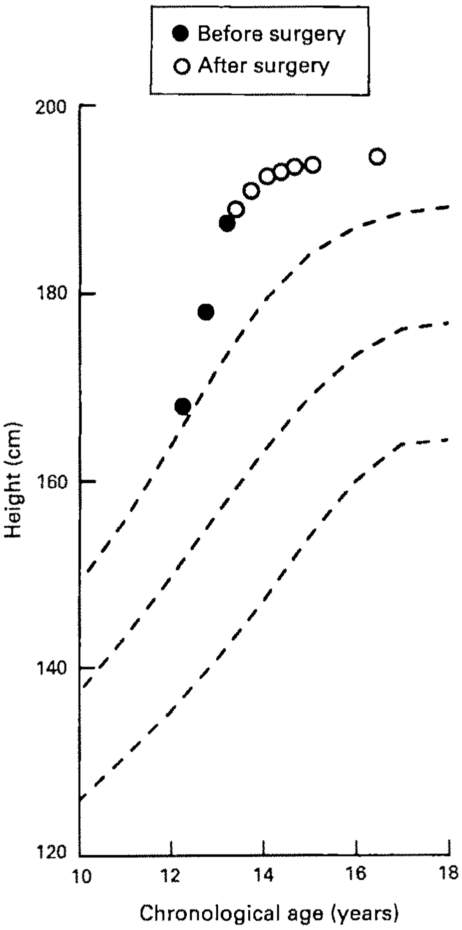

Figure 3 The height measurements obtained before and after surgery were plotted on a male growth chart with the 3rd, 50th, and 97th centiles shown.

spontaneous growth hormone secretion was performed 15 months after the adenomectomy. The mean growth hormone was 4·2 μg/l and again showed a normal growth hormone secretory pattern (fig 2). Five growth hormone pulses were defined by PULSAR algorithm on both occasions. IGF-I remained normal (65·8 nmol/l). Three years after adenomectomy, the IGF-I value (40·2 nmol/l) still remained normal.

GROWTH

In view of an estimated mature height of 214 cm, intramuscular injections of testosterone enanthate (500 mg) were given every two weeks starting three months after surgery. This treatment was continued for 10 months and was then stopped on the basis of relatively mature bone age (16·5 years by the Greulich-Pyle standard), giving an improved estimated mature height of 195·5 cm. He has been followed up at yearly intervals. The most recent clinic visit was three years after surgery when he was 16·5 years of age. His height was 194·6 cm (height SD score 2·9) and he had grown only 1·2 cm in the preceding 15 months (fig 3). Magnetic resonance imaging scans, performed at yearly intervals, have shown no recurrence of the adenoma. He is not receiving any hormonal supplement.

Discussion

Excessive growth hormone secretion causes rapid growth and gigantism in childhood. The endogenous growth hormone secretion of our patient before surgery was characterised by increase in growth hormone throughout the sampling period with no interpulse return to baseline, nor any clearly defined pulses. This is similar to reports of a gigantic patient by Hindmarsh *et al.*[3]

A pituitary adenoma which secretes growth hormone is a rare cause of tall stature and the literature available is limited. Ritzen *et al* reported a case of pituitary gigantism whose growth hormone production, assessed by pharmacological stimulation tests, remained abnormal after transsphenoïdal surgery and the patient subsequently required bromocriptine.[4] By measuring endogenous growth hormone at two hour intervals over a period of 14 hours, Arafah *et al* documented one out of three patients with pituitary gigantism and 11 out of 25 had normalisation of growth hormone secretion after transsphenoidal surgery alone.[5] It is considered that patients with growth hormone secreting tumours usually require additional treatment such as radiation and bromocriptine after surgery. Our patient clearly demonstrated normal pulsatile growth hormone secretion, assessed by frequent blood sampling at 20 minute intervals on two occasions after surgery. In addition, his IGF-I values have been normal during the three years of follow up. This suggests that the hypothalamus in this case was not involved in the pathogenesis of the pituitary adenoma. This differs from a previous report in which a marked increase in the frequency of growth hormone secretory pulses was observed in acromegalic patients.[6]

In conclusion, this is the first report of a patient with pituitary gigantism in whom successful removal of a pituitary adenoma has been documented both clinically and biochemically with normalisation of IGF-I and endogenous growth hormone secretion, assessed by frequent samples. No adverse consequences of the surgical procedure were seen in this case. Furthermore, management of tall stature by the use of testosterone therapy was also successful, the patient's final height being 20 cm less than the initial height prediction before surgery.

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Archives of Disease in Childhood 1992; 67: 1042–1045

CHALLENGES

Paediatric care in Hungary

Dezsö Schuler

This is the fifth paper in a series showing the problems facing the medical services for children in different countries.

Child health in Hungary has historically been an important priority. Hungary was a pioneer in inaugurating obligatory vaccination against smallpox in 1876. The fourth paediatric hospital was founded in Budapest in 1844, after Paris, St Petersburg, and Vienna. It is interesting too to note that the second paediatric hospital in England was founded in 1856 by Whitehead and Schöpf Merei. Schöpf Merei was a Hungarian refugee from a revolution against Austria.

The health care of children in our country is loaded by many problems, the most prominent being limited monetary support and the low sociocultural level, reflected by the fact that only 15·8% of the population has a high school education and 6·4% are graduates from colleges or universities. Before the second world war Hungary was half feudal, half democratic; after the war it became communist. The medical care budget in Hungary is £80 per person per year; in contrast, it is £1100 per person per year in the United States.

The most urgent problems facing Hungarians are: (1) the high infant mortality; (2) the limitations attending cardiac surgery, especially paediatric cardiac surgery; (3) the lack of modern diagnostic tools, particularly magnetic resonance imaging and computed tomography; (4) the unavailability of certain life saving transplantation procedures, for example, bone marrow and liver; (5) the lack of overnight facilities for parents in most hospitals; (6) problems of child welfare and mental health; and (7) the need to overhaul the medical care system emphasising preventive and curative care, and to find the most suitable method of financing and organising it to adapt to the new democratic structure.

Infant mortality

Infant mortality has decreased from 32 per 1000 to 14·8 per 1000 in the past 15 years, but the rate is still unacceptable. The main culprits are the high rate of premature births (9·2%) and the weight-specific mortality, which is also unacceptable, especially in very low birthweight infants. Smoking, other unfavourable kinds of behaviour, the number of previously induced abortions, and lack of prenatal education and care have all been implicated as causes of premature births.

Although pregnant women receive benefits for prenatal consultations, behaviour during pregnancy has improved only slightly. Contraceptive education is not readily available in schools. The importance of a suitable time interval between pregnancies is almost unknown among young women. Counselling after artificially induced abortion is mandatory, but is seldom practiced.

Even educated and cultured Hungarians do not readily accept current contraception information; in most families the responsibility of birth control is left entirely to the woman. Hence despite the availability of oral contraceptives and condoms, 38·6% of pregnancies are aborted. This is unethical, has an unfavourable psychological effect on the mothers, and is disadvantageous in relation to the outcome of the next pregnancy. Permission for induced abortion is not difficult to obtain. Criteria include two children already in the family, genetic problems, social indications, and teenage or out of wedlock pregnancy. More stringent restrictions might decrease the number of such abortions.

One severe problem has been the high infant mortality among people in the lower socioeconomic classes. Many gypsies live in extremely poor circumstances. Their appearance in Hungary dates from the 14th century, and their number has increased gradually. It is now estimated that about 5% of the Hungarian population consists of gypsies. However, in a few counties it is between 7% and 10%, particularly in some small villages, whose populations consist almost entirely of gypsies. Gypsy women are reluctant to attend perinatal education classes. In 1970 the infant mortality among gypsies was 116 out of 1000 births, while the national rate was 35·8 out of 1000 births. The medical profession attempted with special care to rectify this unacceptable situation; in 13 counties of the 19 from which data were available in 1990, the infant mortality among gypsies was 22 out of 1000, and the national rate was 14·8 per 1000.

Many factors were responsible for this welcome decrease in infant mortality among gypsies: (1) special attention was given to them by health care visitors, and medical check ups were done more frequently. (2) Resident nurseries are free for poor patients. (3) Vitamins are supplied free for pregnant women and infants. (4) Vaccinations are available in the home if necessary. (5) Education in hygiene and better health habits for adolescents and pregnant women. (6) Special incentives for practitioners and health care visitors. (7) Better education provided by the schools.

Very low birthweight infants need special care, especially in the form of intensive treatment, parenteral nutrition, and respiratory treatment. Between 1960 and 1970, 10 neonatal intensive care units (NICUs) were established

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with governmental support. However, inadequate funding has hampered the organisation of good transport for newborns to these centres, the hiring of sufficient personnel, and the installation and maintenance of equipment. Nine more NICUs in regional hospitals have been opened with local economic support. Their financial problems are highlighted by the estimate of 320 million HF (£2·5 million) needed to bring these units to a medically acceptable level. The scarcity of trained paediatric nurses is a particular problem: one nurse has the responsibility in one shift for an average of four newborns.

Cardiac surgery

The incidence of congenital heart disease in Hungary is one in 200. About 50% of the affected children would need surgical correction during the first year of life. There are now two centres for cardiac surgical intervention: 90% of the surgery in Budapest, at the Semmelweis University, and 10% in Szeged. The Budapest centre is too small and the equipment is inadequate. The turnover in nurses is high because of the patient load. During the summer vacation period, the surgery must shut down because there is no second team. Although the surgeons are well trained, the lack of facilities is a limitation. The waiting time for open heart surgery is about one year.

Modern diagnostic tools

The new imaging techniques are essential in paediatric diagnosis, but there are only two magnetic resonance imaging units in the entire country, which has a population of 10·6 million. In the diagnosis of brain tumours, for example, magnetic resonance imaging would be extremely valuable. Ultrasound imaging is available and there are now 13 computed tomography facilities; the waiting time for such an examination is 10 to 15 days. More computed tomography and magnetic resonance imaging equipment is urgently needed for adequate diagnostic work. Fortunately, children usually get priority in urgent cases.

Transplantation

Before 1991 there were only two bone marrow transplantation units in Hungary: one with two beds and one with four, all for adults. In December of that year a unit with two sterile tents was opened to care for immunodeficient children. Clearly the problem of bone marrow transplantation in children is a serious and as yet unresolved one. A new unit, with three sterile beds, is now under construction and should be ready to operate in 1993. Until then most of our children are obliged to go abroad for transplantation, an expensive proposition for Hungarian citizens, as health insurance covers only about a tenth of the cost. The rest is paid by the parents or by foundations.

So far no successful liver transplantation has been performed in Hungary. Renal transplantation is well organised, but the waiting time for a cadaver donor is usually one to two years.

Parents' stay in hospital

There are few opportunities for parents to stay with their children in hospitals. There are no Ronald McDonald Houses, as there are in several Western countries, and there are only a few institutions where parents can stay overnight with their sick children. Furthermore, rent in the cities is exorbitant. In our institution, which has 230 beds and houses a national oncology centre as well, there are only three rooms with beds for children and their parents.

Child welfare and mental health

Working mothers with children younger than 3 years of age can remain at home, they receive financial support at the place of employment, and their jobs are kept open for them. However, this option is becoming more difficult because of the worsening economic situation of most families. Despite this situation, the number of infants in day care centres has not increased.

The state grants custody, either in institutions or to foster parents, of children who are not or cannot be cared for by their parents or who need protection. Although the number of children at risk is increasing, the number of children in the custody of the state is diminishing; it is now 0·97%. Thus more parents or other relatives care for the children, with some social and psychological assistance. In 1988 foster parents were granted custody of 29·4% of these children. In the main, their care in such foster families is satisfactory. Of children cared for in institutions, fewer are attending secondary schools or universities (1·26% compared with 3·02% of children in foster families). The result is that beginning a career or finding a suitable occupation is difficult. Adoption, an appropriate solution for children in need, became slightly easier in 1990, but it is far from ideal: at the end of 1989 there were 1737 couples waiting for children to adopt.

Mental health clinics and other centres are run by volunteers and school psychologists. There are consultation centres for the parents of troubled schoolchildren, and in severe cases (12%) these children can be seen in psychiatric outpatient clinics.

The great mental health problems are developmental retardation, particularly in reading, attention, and orientation; adaptation difficulties; emotional disturbances; and attempted suicide, which has been a problem for centuries. Hungary has one of the highest suicide rates in the world. In 1970 the incidence of suicide among adolescents 15 to 25 years of age was 19·2 per 100 000 population; by 1990 it has decreased to 13·6 in 100 000.

Family help centres handle four million cases, that is, 38% of the entire national population. Rearing consultation centres handle 80 000 schoolchildren (3·9%), and child psychiatric outpatient clinics 30 000 (1·4% of schoolchildren). The most severe pathological patients are cared for in 'educational establishments'. The number of psychologists is completely inadequate to the task.

Families are now trying to cope with additional stresses: unemployment is increasing; in

1987 the number of unemployed was 6400, and in 1991 it was approximately 300 000. Because of inflation the real income of most families is rapidly decreasing. There is less job security, and the value of pensions is also decreasing. The rate of divorce has remained on a plateau, but its costs are still isolation, alienation, and single parent families.

The rate of accidents among children is decreasing. In 1970 it was 0·19 per 1000. In 1980 it was 0·14 per 1000, and in 1989 it was 0·12 per 1000. Its prevention is a challenge. Drug abuse, estimated to be 1% among children, has not yet emerged as a serious problem. Child abuse, as in other countries, is difficult to measure, as it frequently goes undetected or unreported.

The changing health care system

The changing economic and political system in Hungary, as well as the advances in medicine, has mandated a reorganisation of the health care system. Until recently the entire medical network—primary care, specialists, consultation centres, and hospitals—was supported by the state, that is, the Ministry of Welfare, and the health budgets of cities and counties. This support was independent of the quality and quantity of care, although from time to time inspections and audits were made by the chief paediatric administrator of the county or the National Institute of Paediatrics, and recommendations for the improvement of local health care were relayed to the appropriate authorities.

Special programmes, such as neonatal intensive care units, cardiac surgery, and paediatric oncology, were supported by the Minstry of Welfare.

In the cities and larger villages, the primary care of children younger than 14 years was provided by paediatricians; 40% of the children, who lived in smaller municipalities, were cared for by general practitioners. Both paediatricians and general practitioners were aided by health visitors, who counselled and educated pregnant women and their families concerning general hygiene, vaccinations, nutrition, and child rearing. Health care visitors also made regular home visits.

Responsibility for primary care now rests with local autonomic authorities, who appoint the physicians and health visitors. Beginning in 1992, the income of primary care physicians will depend on the number of patients registered with them and on the quality of the care, to be financed by health insurance. Family doctoring will be a specialty. Medical school graduates, general practitioners, and paediatricians can qualify as a family doctor after training and an examination. The Semmelweis Medical School recently established a chair for this specialty.

Primary care physicians may be solo general practitioners, family doctors, paediatricians, or members of group practices. Parents have the choice of registering their children with either a family physician or a paediatrician. In the meantime, medical schools should include more studies in paediatric and internal medicine in their curricula.

The predominant objective of the new system is to stimulate better preventive care of the whole family and better primary care of disabled or chronically ill persons, as well as children in need. However, the transition is not easy, as full time private practice has been unknown in Hungary for the last 40 years. In addition, too much time was consumed by administrative work rather than acutal medical practice.

The role of health visitors should also be better defined. Their activities during pregnancy and after delivery have helped to guarantee that every pregnant woman and new mother will receive assistance and advice on rearing their children. It is also imperative that every infant, including those in the lowest socioeconomic categories, receive the attention of health visitors.

Previously every primary care paediatrician had two health visitors working with him or her, and every general practitioner caring for children had one such visitor. In the new system, it is possible that children living in the same geographic area will be cared for by different physicians. The health visitors, however, should work in the same area where they worked before. In this way those children whose parents do not attend welfare clinics should also be cared for by health visitors. On the other hand they will work together with several primary care doctors. This extra workload for the health visitors means a danger that the exchange of information between them and primary care doctors will suffer.

Administration of the health visitors will be handled by the chief health visitor in the county and the counties medical office. However, they should maintain close ties with the primary care physicians. One health visitor now ordinarily cares for about 483 children (including 139 infants), but of course the number varies according to the sociocultural level of the region.

The new method of financing medical care according to its quantity and quality may improve the extremely low income of physicians. The monthly net income of a physician, without overtime pay for night service, ranges from 15·000 to 25·000 HF, the equivalent of $200 to $300 in the United States. Most physicians therefore have a low standard of living, unless their spouses also work outside the home. As a result many physicians, sometimes the best practitioners, prefer to work abroad for long periods of time or gravitate to the pharmaceutical companies with their better pay structures. It is feared that this may constitute a 'brain drain', and that young medical graduates will be discouraged from entering clinical, research, and teaching positions.

Research grants are also inadequate financially. The results are that necessary equipment and the hiring of competent technicians are only rarely possible. In the past year only a few grant applications were accepted by the Ministry of Welfare, with the maximum funding equivalent to $12.000 a year.

Summary and conclusions

In this overview, I have attempted to highlight the problems of medical care, particularly paediatric care, in Hungary and to describe the changing nature of its organisation and financing. We hope that through our efforts we can surmount these difficulties, improve the quality of medical care in our country, and create a more rational economic and scientific basis for future medical development and advances.

Maternal diabetes and the fetal heart

It has been known for 16 years that maternal diabetes may be associated with hypertrophy of the cardiac interventricular septum in the fetus. Two recent reports provide further information about the association.

A study from Cleveland, Ohio (Jean-Claude Veille and colleagues, *Obstetrics and Gynecology* 1992;**79**:51–4) provides information about 64 diabetic pregnancies and 61 controls. Septal thickness measured by echocardiography was significantly greater in the fetuses of diabetic women than in controls at all gestations from 20 weeks upwards. In the diabetic group the hearts were bigger overall but the hypertrophy of the septum was relatively greater than the increase in total heart size or of the ventricular wall. Seventy five percent of the fetuses had septal hypertrophy (more than 2SD above the mean for controls of the same gestational age). One fetus died in utero soon after the demonstration of very marked septal hypertrophy. Twenty two women had glycated haemoglobin measured and there was a correlation between glycated haemoglobin concentrations and septal thickness ($r=0{\cdot}49$, $p=0{\cdot}05$).

Workers in California (Michael J Cooper and colleagues, *American Journal of Diseases of Children* 1992;**146**:226–9) studied 61 pregnant diabetic mothers who were followed up to delivery at 36 or more weeks' gestation. Using more restrictive criteria for diagnosis they found the incidence of septal hypertrophy at birth to be 31%. Their data also differ from the Ohio findings in that they did not find significant increases in septal size before 31 weeks' gestation, a finding perhaps in part explained by the fact that they did not have a control group but compared their findings throughout pregnancy in those who after birth had septal hypertrophy by standard criteria and those who did not. This study provides more detailed information about the relationship between septal hypertrophy and diabetic control.

The mothers of babies with septal hypertrophy had significantly higher glycated haemoglobin concentrations in the third but not in the first or second trimesters. The babies with septal hypertrophy were significantly heavier and had lower blood glucose concentrations postnatally and higher cord blood C peptide concentrations than those without it.

The septal hypertrophy apparently resolves in the first year of life and rarely causes symptoms, although it has been suggested that it may be associated with persistent pulmonary hypertension and idiopathic respiratory distress syndrome. Its main significance seems to be as yet another indicator of poor diabetic control in pregnancy.

ARCHIVIST

Archives of Disease in Childhood 1992; 67: 1046–1049

TYPES OF PSYCHIATRIC TREATMENT

Paediatric liaison

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This is the seventh in a series of articles in treatment of child psychiatric disorders.

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The department of child psychiatry at Booth Hall Children's Hospital in north Manchester was founded in 1953. Although it has always been an integral part of the hospital, the fact that referrals came from a region of over four million people meant that sometimes referrals from the hospital had to take their place in a very long queue.

Over the years the service has changed, staff have developed new skills, but new problems have arisen. A paediatric liaison service must remain flexible and responsive to new challenges. In my view, the best advice that has been given is to 'be available, be practical, and be understandable'.[1]

Availability

Being available meant that as a first priority the non-urgent outpatient waiting list was reduced to manageable proportions, even if that meant discouraging referrals from other districts, where there was a competent service, unless there was a definite request for a second opinion. One of my aims was, therefore, to encourage the development of district services throughout the region, even though this meant that the number of consultants in child psychiatry at Booth Hall remained the same throughout the years (1968–89) that I was there. With the knowledge that a non-urgent referral could be dealt with reasonably promptly, a paediatrician would not be tempted to admit a child for a spurious reason to circumvent the waiting list.

Another measure to increase availability was the provision of a rota, whereby a member of the junior staff and a social worker would be able to assess all children admitted with self poisoning within 24 hours of them regaining consciousness. Urgent requests for help with a diagnostic problem in a child, who was an inpatient, were responded to within 48 hours, by either a consultant or senior registrar. A summary of the essential findings and recommendations would be written in the paediatric casenotes immediately after the assessment.

The apparent availability of the child psychiatrists was heightened by taking an active part in the division of paediatrics, attending paediatric postgraduate meetings and by the simple, but effective, measure of having lunch with the other members of the medical staff.

Priorities

The way in which a paediatric liaison service is organised is liable to vary with the personal interests and expertise of the child psychiatrists concerned, and what is practicable in a given situation. There were several requests for combined ward rounds and joint clinics, but in the early years this was rarely done, mainly on account of pressure of time.

LIMITED INVOLVEMENT IN CHILD ABUSE

At the beginning of the 1970s a decision was made not to get very involved in the management and treatment of families where there was suspected child abuse. At the time, the National Society for the Prevention of Cruelty to Children had set up a special unit in Manchester to offer a comprehensive service to these families and it was thought that they would be able to offer more than we were able to. This was obviously different from the decision made in Oxford.[2] The rise in the recognition of sexual abuse in the 1980s and the increase in referrals of children with emotional and behavioural problems, where abuse was an important factor, forced us to reconsider this decision.

SELF POISONING IN ADOLESCENTS

The sharp rise in the number of children admitted with self poisoning, during the 1970s, left us with no option but to respond promptly and effectively. It was our policy that no child should leave the hospital without themselves being seen by the doctor, who would be responsible for following them up. A member of the child's family would also be seen, before discharge, in order to encourage future involvement with the child psychiatric team if this was thought to be necessary.[3]

RESPONDING TO CHANGING NEEDS AND EXPECTATIONS

Between these extremes of full involvement in what is commonly regarded as the true province of the psychiatrist, as with attempted suicide, and disengagement from what could be seen as exclusively the province of the social worker and paediatrician, as with physical child abuse, there remained the decision as to how best to respond to other requests for help. These were mainly requests for assistance with the diagnosis of a sick child, help in the management of the common disorders of childhood, which are known to have a psychological component, and referrals of children with prolonged and sometimes disabling disorders such as epilepsy, diabetes, asthma, and cystic fibrosis.

Staff on the burns and neurosurgical units also needed support and guidance in the best ways to help families whose child had been severely injured. Likewise, at a later stage, staff on the intensive care unit felt in need of training as how best to cope with their own feelings about being constantly in touch with dying children and their families.

The child psychiatrist needed to be able to provide help to the individual child and to his or her carers. There was also a need to teach staff how to recognise a psychological problem and how to become more aware of their own reactions in stressful situations.

Paediatricians and their supporting staff needed to know how to handle a referral to a child psychiatrist or psychologist and how to improve their ability to treat common problems, so that some referrals may be no longer necessary.

Requests for help with diagnosis

THE REFERRAL PROCESS

Referrals for help with a diagnosis remained the principal component of our liaison service. This type of referral is best carried out at senior level and it is essential that the paediatrician or their senior registrar have discussed the referral with the parents and the child, if old enough, beforehand.

Psychiatry still caries a stigma in the mind of the average person and it is here that the paediatrician's trust in the psychiatrist to whom he or she is going to refer is vital. An explanation that anxieties can sometimes give rise to pain that is genuinely felt should dispel the notion that the child is thought to be a liar or a fraud.

Similarly it is important to help parents to see that referral to a child psychiatrist does not necessarily mean that their child is mentally ill or that the report will form part of a child's school record. As far as the child is concerned, the doctor is one who talks to children about worries and problems. Children are encouraged to know that no painful procedures, such as injections, will be given.

THE PSYCHIATRIC ASSESSMENT

The process of psychiatric interviewing is of necessity detailed and should not be rushed. As well as one or two interviews with the child, there must be at least one with a parent, preferably both. Psychiatrists are trained to make a positive psychiatric diagnosis and not to rely solely on the absence of physiological signs. With children, this will mean an understanding of the dynamics of the family and whether or not a symptom is being used for a secondary gain.[4 5]

Prompt and confident psychiatric diagnosis may spare a child unnecessary investigative procedures and shorten the period of disability.[6] When the issues are less clear, paediatrician and child psychiatrist may continue to work closely together, perhaps during an inpatient assessment, either in a paediatric ward or in a child psychiatric inpatient unit.

Requests for help with common disorders

ENURESIS

Referrals of children with enuresis, encopresis, and sleep disorders were very common 20 years ago. The improvements in available treatment techniques have meant that only the most intractable now reach a child psychiatric clinic. Children with enuresis, who are thought not to have a physical problem, are either dealt with in primary care or their treatment programme is supervised by a clinical psychologist. This is entirely appropriate as children with monosymptomatic enuresis should not be considered to have a psychiatric disorder.[7]

ENCOPRESIS

Encopresis, which is not associated with any physical disorder, is sometimes associated with other behaviour problems and may warrant a full psychiatric assessment. Nevertheless, many cases can be dealt with symptomatically, especially those thought to be due to the withholding of faeces, for whatever reason. Behavioural treatments have proved the most effective and can be administered by a psychologist or a suitably trained community nurse, though most studies have shown that a prolonged follow up is essential.[8]

SLEEPING PROBLEMS

The improvement in methods of helping the parents of young children with sleeping problems[9] has meant that health visitors now feel more competent to treat these disorders in primary care. In some areas sleep clinics have been established to give support and advice to parents with unusually fretful and wakeful children.

One of my priorities over the years was to help health visitors to understand the factors that often underlie some of the common behavioural problems in young children and some basic principles for tackling them.[10]

Children with disabling disorders

The referral of children who are having a particular problem in coming to terms with some aspect of a chronic illness or handicap is often an appropriate referral to a child psychiatric service. For instance the presence of family conflict and dissatisfaction on the part of the mother with her marriage has been shown to relate to poor diabetic control in the child.[11] Likewise, family problems may exacerbate the severity of symptoms in some asthmatic children.[12]

Adolescents also become extremely sensitive about physical disfigurements that previously they had seemed to take in their stride. Similar problems are experienced by epileptic children. The problems may manifest themselves in different ways: depression, school avoidance, or behavioural change. Much will depend on what significance the disease process or handicap has for the child and his or her family.[13 14]

Although services now exist for most of these groups, providing peer support for children and their parents, some children benefit from individual supportive psychotherapy and others from family therapy. Most can be dealt with in the main outpatient service. Joint clinics can be helpful, especially if a clinic is set aside where patients, who both a paediatrician and child psychiatrist have in common, can be seen together, but we did not have these very often.

Services to regional specialist units

At Booth Hall there are regional services for the treatment of burns, a renal dialysis unit, and departments of neurosurgery and neurology. Because of the severity of the children's problems and the way in which their behaviours often caused a great deal of anxiety to the nursing staff, these units were the first to demand, and for some of the time to get, their own direct liaison with either a child psychiatrist or a clinical psychologist.

BURNS UNIT

The direct liaison provided by a clinical psychologist to the burns unit enabled the staff to see the trauma as affecting the whole family and not only the child patient. Supporting the family with the feelings of guilt and helplessness was as important as encouraging the child to come to terms with their disfigurement.[15] Referrals to the child psychiatrist would then only be made when a child was severely behaviourally disturbed, in a toxic confusional state, or unusually depressed and withdrawn.

NEUROSURGICAL UNIT

Similarly, the neurosurgical unit had a clinical psychologist with a sessional attachment, which meant that the common sequelae of children with head injuries were clearly understood by the staff and the expected difficulties communicated to both the parents and the child's school teachers on discharge. The children who were referred on to our department usually had very severe injuries and a pre-existing psychiatric disorder.

RENAL UNIT

My colleague Elena Garralda undertook to have a liaison role with the renal unit. She was able to attend ward meetings and became a significant member of the team. Psychiatric assessment of the children showed that more definite psychological difficulties occurred in those children with the most severe illness. However, psychiatric disturbance was again related to stress in the family and compliance with drug treatment.[16]

NEUROLOGY UNIT

A major part of our liaison work was in the neurology department. It became common practice for the neurologist to discuss a case with one of us, before admission, when a combined assessment was thought to be important. The agreement of suitable dates for the child's admission was then possible. Frequently such patients were treated jointly on the medical ward.[17]

FOLLOW UP

Most of these referrals from the specialist units involved children who lived outside the district. Follow up was therefore sometimes difficult, though parents were often prepared to travel considerable distances at their own expense. It was, however, rarely thought appropriate to refer children to the local child psychiatric service when they had not been involved in any of the inpatient treatment. We suspect that such referrals would not have been taken up by the families. This has major staffing implications for specialised teaching units who wish to encourage a closer child psychiatric liaison.

Teaching

The essence of good teaching is to make the subject understandable. Psychiatrists are well known for using jargon only understood by the initiated. Writing reports and letters in a way that makes sense to the average intelligent doctor is a good way of teaching one's subject and should not be underestimated. Whenever possible our department's assessment and recommendations for treatment would be put in letter form addressed to the paediatrician or relevant consultant and a copy sent to the family doctor.

POSTGRADUATE

Attending clinical meetings and participating in postgraduate training in paediatrics was a regular part of our work. Our monthly child psychiatric case conference was held in the postgraduate centre and was available to all. From time to time we were also able to suggest speakers for day conferences on such themes as the care of the dying child.

UNDERGRADUATE

The clinical teaching of child psychiatry to undergraduates took place in their paediatric placement.[18] As well as attending outpatient clinics and seeing videotaped interviews with child psychiatric patients they also attended weekly seminars, taken by the senior staff, in which they were asked to present cases they had seen. Four of the students would be asked to present a paediatric case from a psychosocial point of view. Most had difficulty with the concept at first, as they had the patients neatly compartmentalised into paediatric and psychiatric.

The aim was to help them to look at such issues as to how a family with a child with a life threatening disease copes or why a baby with a chest infection has not been visited. Sometimes the group would be stimulated to look at deeper issues as to how they felt about the death of a child and how they would help a family come to terms with the birth of a handicapped child.

Conclusion

This account of the development of a paediatric liaison service to a specialist children's hospital in north Manchester does not detail every kind of case we saw. We estimated that approximately 25% of our referrals came from our own hospital. Because of our commitments to more than one district service and a supradistrict child psychiatric inpatient unit our services were inevitably stretched.

As the service developed it has been possible for clinical psychologists to take on the direct liaison with some specialist units, thereby helping the nursing staff to have a better understanding of the emotional and behavioural problems of their patients. Likewise the outcome of a regular clinic between one of the paediatric surgeons and a child psychiatrist was the establishment of a district nursing service for children with encopresis. It is essential that in this type of service all disciplines can refer to each other and that communication between them is easy. The welfare of the child is more important than keeping to rigid professional boundaries. To a large extent a service will develop according to the resources available.

There are many advantages to child psychiatrists in being part of a paediatric service. We were kept up to date in the paediatric field and we hope that the frequent exposure to their influence and scientific rigour prevented us from becoming too set in our ways or inclined to make extravagant claims for our specialty.

In return, we hope that they have gained from our insistence on seeing the child and his or her disease or handicap in the context of their level of understanding, and their life experience, and their family situation. As our knowledge base has increased, and treatment techniques have become more specific, we hope that a basic understanding of our specialty will be a part of every paediatrician's training.

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Archives of Disease in Childhood 1992, 67: 1050–1055

CURRENT TOPIC

Cerebral palsy—an increasing contributor to severe mental retardation?

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Severe mental retardation (SMR), here approximating to an intelligence quotient (IQ) of less than 50, has a prevalence among school entrants of about 3·5 per thousand.[1] The wide range of clinical conditions within the severely retarded population fall into five major groups: Down's syndrome, cerebral palsy, X linked mental retardation, single gene defects, and malformation syndromes. The aim of this paper is to predict the future contribution of the aetiologically heterogeneous group of cerebral palsy to the severely retarded population.

The prevalence of cerebral palsy is about 2/1000 in most childhood populations studied,[2] and up to 35% of those affected (0·7/1000), are also severely mentally retarded[3 4] (G Hagberg, personal communication). This group therefore comprises about one fifth of the overall prevalence of severe mental retardation. For comparison, Down's syndrome contributes one third and X linked mental retardation, single gene defects, and malformation syndromes each contribute one tenth to the overall prevalence.

Background information needed to predict future trends in this group includes a knowledge of the causes of cerebral palsy, and of any trends in their prevalence; and of the effect of changes in the early mortality rates of affected or high risk infants. Although in most cases the cause remains unknown, associated factors are recognised and will be used for prediction.

As only few reports of cerebral palsy distinguish between the characteristics of those with SMR and those without, the literature on trends in cerebral palsy in general will be reviewed, pointing out any factors known to be particularly related to SMR.

Associated factors

One feature which distinguishes the epidemiology of cerebral palsy from that of any of the other causes of SMR is the close association between cerebral palsy and low birth weight, whether in preterm or other births. This relationship acts as an important confounding factor and must be taken into account in any analyses of possible causation, or when predicting trends. It is accepted that many of the adverse obstetric factors known to be associated with cerebral palsy may act primarily by causing preterm delivery, and thus are only indirectly related with the sequelae consequent upon immaturity. Similarly, brain 'damage' may be the cause and not the consequence of asphyxia at birth.

In the following account the likely time of action of different types of insult will be described, but it must be borne in mind that many of these causes may act differently at different ages.

KNOWN PRENATAL CAUSES

Environmental factors that are known to cause prenatal brain injury include congenital infections; exposure to toxins including drugs and alcohol; and a suboptimal uterine environment of unknown cause which has been described as 'fetal deprivation of supply', secondary to a number of known and unknown causes.

Infections

In the UK cytomegalovirus is the most common cause of congenital infection, leading to impairment in about 0·3/1000 births.[5] Approximately half of the affected children have cerebral palsy or psychomotor delay, but not all will have SMR. Isolated mental retardation is uncommon.[6 7] The congenital rubella syndrome currently has a birth prevalence of about 0·03/1000, and reported sequelae include cerebral palsy, but again isolated mental retardation is uncommon. Congenital toxoplasmosis[8] is a cause of severe retardation in the absence of cerebral palsy but birth prevalence is estimated to be less than 0·01/1000. The impact of HIV has yet to be assessed. Evidence is growing that a substantial proportion of symptomatic infected children have neurological syndromes which may involve mental retardation,[9–12] but at present the number of children in the UK known to be HIV positive is very small.

In summary, congenital infections together probably cause no more than an estimated 0·03 cases of SMR/1000 live births, most of which will be associated with cerebral palsy. There is unlikely to be any substantial change in the prevalence of these risks, since it is only congenital rubella, already a rare cause, which is likely to decline further over the next decade. There is a possibility that congenital HIV infections may lead to a small increase.

Alcohol

Although many prescription drugs may cause fetal damage, alcohol is the only commonly used fetal toxin that has been linked to mental retardation, although severe retardation is probably not common. The mean IQ for the fetal alcohol syndrome has been stated to be 63.[13] Estimates of the prevalence of fetal alcohol syndrome, and more specifically mental retardation associated with maternal alcohol intake, are scanty and inconsistent. It seems that in the UK the number of cases of severe retardation due to alcohol consumption is likely to be very small, although good population based data is scanty.[14]

Fetal deprivation of supply (FDS)

This is a term introduced in Scandinavia to include cases of presumed prenatal fetal deprivation inferred from either maternal complications or fetal growth retardation. Often it is not known whether the growth retardation is due to fetal or maternal causes. Estimates from Sweden and Canada indicate that 0·3/1000 cases of SMR are linked to FDS,[15] [16] but it is difficult to tell from the literature how many are associated with cerebral palsy.

Perinatal brain damage

Perinatal brain damage will include the effects on potentially normal babies of complications around the time of birth, including asphyxia and trauma.

For babies of normal birth weight perinatal factors are thought unlikely to be important as a cause of isolated SMR,[16] but it had been hoped that improved obstetric care would lead to a fall in prevalence of cerebral palsy in babies of normal birth weight in parallel with the fall occurring in perinatal mortality. Recent work suggests, however, that birth asphyxia is a rare cause of cerebral palsy,[17] [18] accounting for less than 10% of the total.

In the very low birthweight infant whose chance of survival is increasing, the complications of immaturity may be extremely important in those potentially normal at birth, resulting in periventricular ischaemia and neurological sequelae. However, we do not known in what proportion preterm birth is a consequence of prenatal damage, which itself causes neurological sequelae. Infantile hydrocephalus after cerebral haemorrhage, and its sequelae, is another important cause of SMR and/or cerebral palsy, for which the best recent prevalence data is from Sweden with a rate of 0·63/1000 in the birth years 1979–82.[19–22] The ventriculomegaly trial group in England reported that all affected children with developmental delay also had neuromotor impairments.[23]

Although perinatal damage is traditionally associated with cerebral palsy, some survivors of low birth weight are severely retarded but do not have cerebral palsy. These may have associated sensory deficits such as deafness or blindness or may have isolated SMR. Alberman *et al*, studying births of less than 1814 g born in the 1970s, found that the total prevalence of severe mental retardation was 17/1000 with 14·5/1000 being associated with cerebral palsy.[24] Recent smaller studies report no cases of SMR without cerebral palsy,[25] [26] although in others it is difficult to extract this information.[27]

A 'best guess' for the contribution of perinatal factors to SMR is about 0·3/1000 births, and this proportion is one that may be rising because of the improved survival of high risk infants.

Postnatal brain injury

Causes of postnatal brain injury reflect the hazards of the older child's environment. Infections of the nervous system are predominant but trauma, particularly road traffic accidents and non-accidental injury, are also important. Survivors of central nervous system malignancies also contribute but are a small group, most also having motor deficits. There are many problems associated with definitions of postnatal cerebral palsy, reported prevalence of postnatal SMR varying from 0·1 to 0·5/1000,[1] [15] [28] but this group is one where improved standards of living and better medical care should lead to a reduction. Nevertheless preterm births are at increased risk and their increasing survival must be taken into account when assessing likely trends.

Our 'best guess' for the overall prevalence per thousand children of SMR with cerebral palsy is 0·03 due to congenital infection, 0·3 due to fetal deprivation, 0·3 due to perinatal factors, and the remainder, perhaps 0·2, associated with postnatal factors, with a small proportion due to the fetal alcohol syndrome or other exposure to fetal toxins.

Trends in the prevalence of cerebral palsy

PRENATALLY AND PERINATALLY CAUSED CEREBRAL PALSY

Cerebral palsy registers in Mersey Regional Health Authority in England, in south western Sweden, and in Western Australia provide the bulk of the recent trend data,[29–32] with additional information from registers in the regional health authorities in the north east and south east of England.

The reported overall prevalence per 1000 live births, excluding postnatal cases, remained fairly stable from 1958 to 1977,[2] and then began to rise. Table 1 gives recent data from Sweden, Western Australia and Mersey, and there have been similar reports from elsewhere.[33–35]

The table gives the trends in different birthweight groups and shows that there has been a fairly constant level over time in babies of normal birth weight in the studies included, although Jarvis *et al* found an increase in reported live birth prevalence from 1·03 to 1·53/1000 among babies weighing 2500 to 4000 g between birth years 1968–71 and 1972–5.[36] In all three registers, apart from the most recent Mersey data, there has been a fall in prevalence rates in the group weighing between 1500 and 2499 g at birth.

However, the most striking finding in the table is the considerable rise in prevalence in neonatal survivors found in all three registers for babies of <1500 g birth weight. The most recent data from Mersey suggest that the increase in prevalence in the very smallest babies is maintained, although there have been some recent reports suggesting that the disability rate in these is stable, or falling.[37] [38] Nevertheless, the Mersey and Swedish recent prevalence rates of cerebral palsy in babies of under 1500 g of around 90/1000 are confirmed by numerous

Table 1 International comparisons of cerebral palsy rates/1000 neonatal survivors and percentage of different birth weights (postnatal cases excluded) SEE ADDENDUM *p 1055*

Birth weight (g)	*1971–4 Rate/ 1000*	*%*	*1975–8 Rate/ 1000*	*%*	*1979–82 Rate/ 1000*	*%*	*1983–4 Rate/ 1000*	*%*
Sweden[a30 31]								
<1500	–	–	58·3	9·4	93·3	18·2	–	–
1500–2499	–	–	17·2	31·1	12·6	20·8	–	–
≥2500	–	–	1·2	59·4	1·3	61·0	–	–
Total	1·[illegible]7*		1·91*	100	2·05*	100	–	–
Western Australia[b29]								
<1500	–	–	28·4	5·7	46·1	13·0	76·4	23·2
1500–2499	–	–	12·6	28·5	9·2	22·4	7·3	16·2
≥2500	–	–	1·4	65·8	1·3	64·6	1·4	60·6
Total	1·3*	–	2·10*	100	2·40†	100	2·18	100
Mersey[32]								
<1500	–	–	19·0	4·6	90·7	21·3	81·9	23·6
1500–2499	–	–	10·4	33·1	9·5	27·3	12·8	26·8
≥2500	–	–	1·0	62·3	1·1	51·4	1·0	49·5
Total	1·75*	–	1·51*	–	1·95*	100	1·94*	100
Ireland†[33]								
<1500	–	–	–	–	–	–	–	–
1500–2499	–	–	–	–	–	–	–	–
≥2500	–	–	–	–	–	–	–	–
Total	–	–	1·56*	100	1·89†	100	–	–

*Rate/1000 live births Including data from F Stanley, E Alberman Unpublished report of a meeting of the International Cerebral Palsy Society, Cambridge 1989.
†Years 1976–8 and 1979–81
[a]G Hagberg, personal communication
[b]F Stanley, personal communication.

smaller, but not always population based, studies.[26 27 39 40]

In all developed countries there has been a sharp fall in neonatal mortality, even though many deliveries previously regarded as miscarriages are being resuscitated and registered as live births. A decrease in neonatal mortality rates with constant cerebral palsy prevalence risks in the survivors will inevitably lead to an increase in both absolute numbers and in prevalence rate.

A consequence of these changes in pattern is that babies of under 1500 g form an increasing proportion of the total cerebral palsy cases. Between the periods 1975–8 and 1979–82 this proportion rose from 9·4 to 18·2% in the Swedish data, from 5·7 to 13·0% in the Australian data, and from 4·6 to 21·3% in the Mersey data, which also shows that between 1983 and 1984 these babies accounted for nearly 24% of the total.

POSTNATAL CEREBRAL PALSY

Population based reports from Mersey and Western Australia give the best epidemiological data on cerebral palsy arising after the neonatal period.[41–43] Postnatally acquired cerebral palsy in the industrialised world usually forms approximately 10% of total cases.[4] The recent report from Mersey[43] was unusual in finding that postneonatal cases were responsible for 18% of the total. In this study, between 1966 and 1977 the prevalence rate of postnatally acquired cerebral palsy varied from 0·2 to 0·6/1000 neonatal survivors. The overall figure was 0·3/1000 neonatal survivors. In Western Australia[41 42] prevalence rates varied from 0·19 to 0·27/1000 neonatal survivors between 1956 and 1975.

In Mersey there was evidence that survivors of low birth weight were at higher risk of developing cerebral palsy than babies of normal birth weight, their increased prevalence possibly accounting for the unusually high proportion of postnatal cases. The rates per 1000 neonatal survivors were 0·71 in those of birth weight <1500 g; 0·56 in the birthweight group 1500–2499 g, and 0·31 in those of normal birth weight.

SUMMARY OF PREVALENCE DATA

The prevalence figures from Mersey are the most complete and have been used to estimate future trends (see table 2). The rate of cerebral palsy due to prenatal and perinatal causes in babies of normal birth weight is lower in Mersey than reported elsewhere (table 1) and this may affect results.

SEVERE MENTAL RETARDATION IN CEREBRAL PALSY

Information on mental retardation in cerebral palsy is limited. Table 3 gives data from two studies. Although previously SMR was less common in children of low birth weight and cerebral palsy, recent reports from Sweden indicate that there is a high prevalence of severe retardation among children contributing to the increasing prevalence of cerebral palsy in very low birthweight infants.[28] Although Pharoah *et al* reported a very high incidence of SMR of 57% in postnatal cases,[43] other reports of postnatal cerebral palsy give figures that are closer to those given in table 3 for the prenatal and perinatal cases. For instance Arens and Molteno describe 37% of their postnatal cases as having severe or profound retardation.[44] The assumption is made that 35% of cerebral palsy cases in all birthweight groups in pre/perinatal, and in postnatal cases will have SMR.

Prediction of future trends

Because of the considerable importance of birth weight as a risk factor any prediction of future trends must take into account current and future likely trends in birthweight distribution and survival rates. Data on birthweight distribution and neonatal mortality rate of live births from 1983 to 1988 was supplied by the Office of Population Censuses and Surveys (personal

Table 2 Prevalence rates of cerebral palsy of different aetiology/1000 neonatal survivors of different birthweight groups

Birth weight (g)	*Pre/perinatal aetiology*[1]	*Postnatal aetiology*†	*Total prevalence*
<1500	90·7	0·7	91·4
1500–2499	9·5	0·6	10·1
≥2500	1·1	0·3	1·4

[1]Based on data from Mersey 1979–82 [32]
†Based on data from Mersey 1966–77 [43]

Table 3 Incidence of mental retardation in cerebral palsy children by birthweight groups

Birth weight (g)	*Mersey %SMR*	*Mersey %MMR*	*South East Thames %SMR*	*South East Thames %MMR*
<1500	13	18	29	25
1500–2499	31	17	36	18
≥2500	40	13	37	24
Total	36	14	36	23

SMR, severe mental retardation, MMR, mild mental retardation.
Mersey data for births 1966–77 [4]
South East Thames data for births 1970–79 (P Evans, personal communication).

Table 4 Number of cerebral palsy cases expected from births 1983–8 in England and Wales, assuming prevalence rates from table 2, by time of insult and birth weight

Year	*Total No live births*	*<1500 g*			*1500–2499 g*			*≥2500 g*		
		NNS	*Pre/peri*	*Post*	*NNS*	*Pre/peri*	*Post*	*NNS*	*Pre/peri*	*Post*
1983	639 111	3731	338	3	36 026	342	22	585 035	644	176
1984	636 818	4003	363	3	36 376	346	22	592 277	652	178
1985	656 417	4354	395	3	38 045	361	23	609 685	671	183
1986	661 018	4490	407	3	38 954	370	23	613 606	675	184
1987	681 511	4825	438	3	38 664	367	23	634 211	698	190
1988	693 577	4818	437	3	38 567	366	23	646 049	711	194

NNS, neonatal survivor, Pre/peri, expected cases of cerebral palsy of pre/perinatal aetiology, Post, expected cases of cerebral palsy of postnatal aetiology

communication) and suggest that the proportion of total births that are of low birth weight may have reached a plateau, after rising for some years, and neonatal mortality rates of low birthweight infants are also levelling out after sharp falls. For the births of 2500 g or more neonatal mortality rates are continuing to fall. For the present purpose the conservative assumption has been made that birthweight distributions and the neonatal mortality rates over the next 12 years will level out from 1988, and the 1988 rates will be applied to birth projections for this period.

The importance to the overall prevalence of cerebral palsy of the birthweight distribution of neonatal survivors is demonstrated in table 4. This gives for England and Wales the number of neonatal survivors of known birth weight (over 99% of the total) for the years 1983 to 1988, and applies to them the birthweight group specific cerebral palsy prevalence rates derived from the most recent Mersey data (table 2). Although these prevalence rates in neonatal survivors are kept constant there is a 5% rise in crude prevalence largely because of the increase in the number of neonatal survivors of under 1500 g, with their very high risks. The live birth prevalence of prenatal and perinatal cerebral palsy rises to 2·2/1000 and all cerebral palsy cases reach 2·5/1000 (table 5).

It remains unclear whether any children subject to the insults described above are severely retarded but do not have cerebral palsy. Present indications are that this is the case for very few, if any, severely retarded children. No data are available but a notional birth prevalence of 0·2/1000 for these additional cases is suggested. This group is not included in the subsequent predictions.

DEMOGRAPHIC PROJECTIONS

The total number of live births in England and Wales expected each year from 1990 to the year 2000 was supplied by the Government's Actuary Department (personal communication). Assuming that birthweight distribution, neonatal survival, and cerebral palsy prevalence remain constant from 1988 levels, the future number of cerebral palsy cases was estimated by applying rates of 2·2/1000 live births for prenatal and perinatal cerebral palsy and 2·5/1000 for all cases including postnatal (table 6).

The number of severely retarded children with cerebral palsy was estimated to be 35% of the total overall. The projected number of cerebral palsy cases with SMR, assuming a steady rate of 35%, would fall from a peak of 648 born in 1993 and 1994 to 599 born in 2000, when the number of births is expected to have dropped.

Table 5 Total number of expected cerebral palsy cases and rate/1000 live births derived from table 4

Year	*No of cerebral palsy cases*		*Rate/1000 live births*	
	Pre/peri	*All*	*Pre/peri*	*All*
1983	1324	1525	2 07	2 39
1984	1361	1564	2 14	2 46
1985	1427	1636	2 17	2 49
1986	1452	1662	2 20	2 51
1987	1503	1719	2 20	2 52
1988	1514	1734	2 18	2 50

Associated impairments and survival

Details of severely retarded children with cerebral palsy are scarce and data from South East Thames and North East Thames cerebral palsy registers gives some picture of these children (P Evans, personal communication). Data from the North East Thames register is still being collected and information regarding mental ability is very incomplete so that results must be viewed with caution. Table 7 gives details of associated impairments in the severely retarded children. Approximately one half have epilepsy and almost two thirds have no useful hand function and are immobile.

SURVIVAL

A recent report[45] from South East Thames indicates that 79% of severely retarded children registered as having a diagnosis of cerebral palsy survived to a mean age of 16 years. Survival rates beyond this age are not available. This is higher than reported previously in an earlier study from the US.[46] Multivariate analysis of deaths in all mental abilities in the South East Thames data showed that immobility was the strongest predictor for mortality, followed by

Table 6 Predicted number of cerebral palsy cases from births 1990–2000 in England and Wales: constant prevalence rates

Year	*Total No live births*	*Pre/perinatal cases*	*All cases*	*Cerebral palsy and SMR*
1990	725 626	1596	1814	635
1991	732 528	1612	1831	641
1992	737 681	1623	1844	645
1993	740 491-	1629	1851	648
1994	740 229	1628	1851	648
1995	736 834	1621	1842	645
1996	729 849	1606	1825	639
1997	719 618	1583	1799	630
1998	709 397	1561	1773	621
1999	696 541	1532	1741	609
2000	684 917	1507	1712	599

SMR, severe mental retardation.

Table 7 Associated impairments in children with cerebral palsy and severe mental retardation. Figures are percentages

Impairment	*South East Thames*[†] *(n=189)*	*North East Thames*[†] *(n=69)*
Seizures	51 3	49 2
Hearing	11 8	16 7
Vision	68 9	53 0
Ambulant with or without aids	36 2	24 4
Chair/bed ridden	62·4	65 9
(self propelled)	(2 5)	(4 9)
Severely limited manual dexterity	65 2	59 4

[†] P Evans, personal communication

severe retardation: 31% of the immobile, severely retarded group had died compared with 3% of the mobile but severely retarded group.

Discussion

PREDICTIONS

The most recent data upon which these predictions have been based come from births up to 1984. When calculating future prevalence it has been assumed that prevalence rates will stay at the these levels. It is important to consider any possible changes that may challenge this assumption.

BIRTHS UNDER 1500 G: PREVALENCE AND SURVIVAL

The predictions made have taken into account trends in the prevalence of the high risk birthweight groups up to 1988 only. It is possible that following the alteration in the abortion law, lowering the upper limit at which legal termination is permitted to 24 weeks, the legal distinction between stillbirth and miscarriage will also be changed to 24 weeks. This may have an effect in further increasing the resuscitation of births less than 1500 g.

A focus of recent literature on this question has been how much of the increase in prevalence of cerebral palsy in these babies is due to increased survival of prenatally impaired children, and how much to postnatal damage during their neonatal course.[31] [32] The latter situation leaves more scope for improvement with better neonatal care. At present we have little understanding of the prenatal causes leading to preterm birth with permanent neurological sequelae, and no means of preventing them; yet recent work with serial ultrasound has indicated that in one third of children with disabilities, ischaemic brain lesions were noted within two hours of birth, confirming the hypotheses that some of this damage had taken place before or during birth.[47] Advances in medical imaging will continue to improve our knowledge of the timing of the insult in this group.

Regardless of timing, many studies have shown that periventricular leucomalacia and ventricular enlargement are predictors of future handicap.[25] [26] [48] [49] Early recognition of severely damaged infants may lead to a reconsideration of their neonatal management, with a reduction in effort to maintain their survival. This may lead to a fall in both neonatal survival and cerebral palsy prevalence in those survivors.

BIRTHS WEIGHING BETWEEN 1500 AND 2499 G

This is a group about which little is known in regard to timing of insult, although their survival has improved considerably. It is likely, although not certain, that in many such affected births there has been a prenatal insult, but they probably include a group which resembles the very low birthweight group in their stormy neonatal course. It is difficult to predict whether there are likely to be changes in risk exposure affecting the prevalence of SMR, other than purely demographic, which have been taken into account. The assumption has been that there will be no such changes over the next decade.

BIRTHS GREATER THAN 2499 G

Since imaging is less often carried out in larger babies, and many will develop cerebral palsy after an apparently normal obstetric and neonatal course, the literature on the timing of the insult is usually based on inference only. It is now recognised that birth asphyxia plays only a small part, and probably 90% are due to prenatal causes, most of which are not preventable in our present state of knowledge. Fetal deprivation of supply is so poorly understood that substantial reduction seems unlikely. HIV infection may prove increasingly important but further reduction in the number of cases of rubella or of infants damaged by cytomegalovirus is unlikely. Increasing public awareness may reduce the problems of alcohol but this is unlikely to have a major impact on total prevalence of SMR.

The assumption has been made that over the next decade the risk in these babies is likely to stay constant, and that changes are likely to be accounted for by demographic changes only.

POSTNATAL CEREBRAL PALSY AND SMR

Work published on postnatally acquired cerebral palsy is largely based on data from the 1950s to 1970s. The population studies on SMR giving prevalence of postnatal SMR are of the same era. Changes in medical care and child safety may make these results unreliable as a basis for future prediction. Infection is the leading cause of postnatal cerebral palsy in all studies, particularly meningitis and encephalitis. Gastroenteritis and subsequent dehydration was responsible for up to 15% of cases. Trauma is the second most common cause accounting for a quarter of cases. Road traffic accidents alone cause almost 10% and non-accidental injury between 3% and 9% of postnatal cerebral palsy. Improvement in parental education so that children's illnesses are recognised and treated sooner may mean that infectious causes are diminished. It seems feasible to assume that the widespread use of safety seats in cars will have reduced the contribution of road traffic accidents to the total. On balance it seems most likely that postnatal causes will be less common than they were, and any fall in this group would imply a reduction in our projected prevalence of 2·5/1000.

Summary

It is estimated that the prevalence of non-genetic SMR associated with cerebral palsy has risen from 0·7 to about 0·9 per 1000 live births in the last decade. This is due to the predicted rise in total cerebral palsy prevalence to 2·5/1000 live births. This predicted prevalence of cerebral palsy is similar to that given for Western Australia in 1979–82, allowing for postnatal causes, but is higher than prevalence data from England and Sweden for that period. The estimated rise is due largely to improved survival and increased proportion of low birthweight babies since 1983 and also reflects the use of prevalence rates based on Mersey data.

Improvements in prenatal diagnosis, and a parental choice of selective termination may lead to reductions in other causes of SMR, such as Down's syndrome and neural tube defects, so it seems that children both physically and mentally handicapped due to brain damage will contribute a greater proportion of the SMR population. The careload of these children is greater than that associated with many other causes of SMR and most survive into adult life. The implications for planning future services will need to be recognised.

Unpublished data and advice from Dr G Hagberg, Dr F Stanley, Ms Linda Watson, and Dr P Evans is gratefully acknowledged The Office of Population Censuses and Surveys and the Government Actuary's Department kindly provided unpublished demographic data The study has been supported by the Department of Health

Addendum

The recent publication of F J Stanley and L Watson (Trends in perinatal mortality and cerebral palsy in Western Australia, 1967 to 1985, *BMJ* 1992;**304**: 1658–63) has shown that there are minor errors in table 1. For Western Australia total prevalence of cerebral palsy per 1000 live births (postnatal causes excluded) for the years 1975–8 and 1979–82 should read 1·92 and 1·88 (not 2·10 and 2·40). Individual birthweight prevalences are correct. Thus our predicted prevalence for all cerebral palsy of 2·5/1000 live births is higher than any previous reports.

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CURRENT TOPIC

Guidelines for management of idiopathic thrombocytopenic purpura

O B Eden, J S Lilleyman on behalf of the British Paediatric Haematology Group

Children with idiopathic (immune) thrombocytopenic purpura (ITP) are almost invariably admitted to hospital for diagnosis. The usual presentation is an acute onset of bruising, purpura and petechiae or, less commonly, with mucosal bleeding from gums, nose, or rectum. Serious mucosal bleeding is unusual in uncomplicated ITP and should provoke a search for other causes. The majority of patients (80%) will provide a history of some infection, usually viral, within the preceding three weeks. The peripheral blood normally shows simple thrombocytopenia without other abnormality, although some idividuals have a modest relative or absolute lymphocytosis. In 75% of cases the platelet count returns to normal within 3 months (90% by 9–12 weeks), but a history of bruising for one to two weeks before diagnosis often suggests a more chronic course is likely.[1–3]

Should bone marrow aspiration be done?

The presence of associated symptoms or signs such as pallor, lassitude, pain (particularly in the abdomen or limbs), a limp, lymphadenopathy, or hepatosplenomegaly should lead to the suspicion of more serious pathology, and in such circumstances bone marrow aspiration is obviously essential. But the majority of patients present just with a short history of bruising, petechiae, or bleeding without other symptoms or signs. They show no pancytopenia and have a blood picture which does not suggest marrow infiltration or aplasia. For such children, provided no treatment is contemplated, urgent marrow examination is probably not necessary, but despite this some clinicans and parents still feel happier if infiltration and aplasia are immediately and absolutely excluded and so perform the procedure on all patients. A legitimate alternative approach is observation without treatment or investigation, especially if the platelet count is above $30\times10^9/l$, and only to perform a bone marrow examination if a child fails to remit within two to three weeks or if treatment, especially with steroids, is contemplated

Other recommended investigations

Childhood ITP is only rarely associated with other immunological disorders. Immunoglobulin concentrations (especially IgA and IgG) are worth measuring, and viral serology can occasionally be informative. Cytomegalovirus infection should be considered in infants un 1 year old (perinatally acquired infection) infectious mononucleosis in older childr Immune thrombocytopenia has been repor as the first manifestation of HIV infection vertically transmitted and blood product a ciated infection. Clinical pointers from history should alert the clinician to the neces for exclusion of this cause of ITP and rou investigation of all patients is clearly required.

There is probably no need regularly perform a Coombs's test or coagulation scr or to look for antinuclear factor (ANF) DNA antibodies. ITP as a feature of syste lupus erythematosus (SLE) is reported m commonly in adolescent girls and is usu associated with other stigmata of the disease is sometimes informative to check patients w chronic disease for these other autoimm disorders.

Finally, platelet antibody tests are surprisin unhelpful for either diagnosis or managem certainly in acute ITP. They may be m useful if the disease progresses to chroni (defined as lasting for more than six mont Platelet associated immunoglobulin assay more helpful; but the test is impossible w very low platelet counts and not readily av able.

Should children with ITP stay in hospital?

Once the diagnosis is confirmed there is usu no justification for keeping a patient in hosp until the platelet count rises. Exceptions dep on bleeding problems or social circumstan and (to a lesser extent) whether the parents be able to prevent fights or vigorous knockab games. The risk of serious bleeding, in partic intracranial haemorrhage, is probably as sr at home as in hospital. Confining children bed or putting severe restrictions on t activity is difficult to achieve, of no pro benefit, and produces boredom in the pat and anxiety in the parents. The risk of in cranial haemorrhage, based on published ser is under 1%, but that risk persists through the time of profound thrombocytopenia (plat count $<10\times10^9/l$).

Treatment—steroids or not?

Only small randomised studies testing stero compared with no treatment have ever b

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possible in ITP. The evidence, such as it is, suggests that those receiving steroids recover their platelet counts slightly faster than those receiving no treatment.[4 5] The essential natural history of the condition does not appear to be influenced by steroids and there is no evidence that steroids reduce the vanishingly low mortality rate.

Low doses of prednisolone (0·25 mg/kg/day) appear to be as effective as higher doses.[6] In order to prevent troublesome side effects, doses over 2 mg/kg/day should definitely be avoided, and the drug should be discontinued after two to three weeks irrespective of the platelet count. For children presenting with bruising only, without mucosal or more severe haemorrhage, no treatment at all is perfectly reasonable. The patient's condition rather than the number of platelets should determine the management. Patients with counts above 30×10^9/l very rarely need any treatment.

Continuation of steroids in full dosage beyond two weeks is unlikely to increase the chance of response if none has been achieved in that first fortnight. A reasonable compromise is to give full dosage for one week only with a gradual reduction in the second week. Cessation of treatment after two weeks is sometimes associated with a dip in platelet count when there has been a good initial response, but usually not to the initial low levels.

The mode of action of steroids principally operative in ITP appears to be inhibition of phagocytosis of sensitised platelets. In the rare patient with very severe persistent thrombocytopenia and symptomatic thrombocytopenia unresponsive to steroids, some believe there may be benefit from low dose treatment (5 mg) on alternate days. This is based on the theory that steroids can stabilise capillary endothelium and may reduce cutaneous bruising. However a decision to continue such treatment long term should not be taken lightly. The most frequent instance of mismanagement in ITP is the use of prolonged courses of steroids, and patients with persistent problems require careful evaluation for other treatment. Long term steroids can impair growth and produce all the well known cushingoid problems, and of course can generate immunosuppression with subsequent major risk from infections such as measles.

Intravenous immunoglobulin

Latterly there has been a vogue for the rapid and liberal use of intravenous high dose human pooled immunoglobulin in children with newly diagnosed ITP.[7] It is hard to justify such an approach. To date there has been only one multicentre trial comparing no treatment, steroids, and intravenous immunoglobulin.[8] In that study immunoglobulin appeared to be slightly better than steroids in shortening the period of profound thrombocytopenia but this was not clinically important. Both appeared to allow a rise in platelet count faster than no treatment. As with steroids there is no evidence at all that immunoglobulin reduces the low mortality of this condition. Recommended doses have been reduced in recent times, but the material is very expensive, requires the patient to stay in hospital for its infusion, and there is still some lingering anxiety about the transmission of non-A non-B hepatitis.[1] A few cases of transient encephalopathic symptoms have also been reported.

For the present it seems reasonable that immunoglobulin should be reserved for: (i) emergency treatment of patients who do not remit or respond to steroids and who present with active bleeding and (ii) if cover is required to enable essential operations or emergency dental extractions to be performed.

Non-remitters and chronic ITP

Chronic ITP is defined as thrombocytopenia persisting beyond six months, and it will arise in 10–20% of patients.[1–3] Such children may still recover spontaneously years after diagnosis irrespective of treatment.[1 3] There is a regrettable tendency to treat platelet counts rather than symptoms, and it should be understood that chronic thrombocytopenia is compatible with normal activity and longevity.[3 9] Most patients and their families simply require reassurance together with avoidance of aspirin and contact sports.[3] If other treatment is considered prior discussion with, or referral to, the regional paediatric haematology team is recommended. The only patients with chronic ITP who need treatment are (a) those with profound thrombocytopenia and repeated muscosal bleeding (particularly epistaxes), (b) older children with menorrhagia, (c) victims of accidental or other trauma, (d) those needing elective surgery, and (e) (obviously) those who develop any acute neurological signs. Profoundly thrombocytopenic patients who develop persistent or recurrent headache should be investigated and, if appropriate, treated aggressively (see below). Chronic ITP patients are the group who warrant investigation for other autoimmune disorders (for example SLE).

As long term steroids have unacceptable side effects, alternative treatments have to be considered in the few children with chronic ITP who need treatment. Pulses of high dose methyl prednisolone (30 mg/kg daily for three days) appear safe and can often temporarily raise platelet counts to cover emergencies.[10] This approach offers a perhaps safer and cheaper alternative to intravenous immunoglobulin which can be used in similar circumstances.

Splenectomy has been used for many years and about two thirds of chronic sufferers will derive permanent benefit,[9 11 12] but it should be remembered that there is a mortality from postsplenectomy infection.[13] The risk of overwhelming sepsis is real, and while greatest in young children (under 5 years),[14] probably persists for life.[15] The mortality from infection after ITP splenectomy is estimated to be 1·4% by Singer,[16] but Eraklis and Filler reported seven deaths out of 262 patients (2·7%).[17] Bearing this in mind, splenectomy should not be considered before at least six months and preferably 12 months from time of diagnosis, unless there are very major problems (see below). Before splenectomy all patients should receive pneumococcal vaccine and commence life long prophylactic penicillin.

Other alternative treatments are legion, but none has yet been shown to be universally effective and/or safe.

Cytotoxic drugs, especially vincristine[18] and azathioprine[19] have been used but cannot be recommended for routine practice. Toxicity may be severe and life threatening.[20] High dose vitamin C,[21] anti-D immunoglobulin,[22] and danazol[23] have recently been tried, primarily in adults. Although it is perhaps premature to comment on their efficacy, preliminary results are not encouraging in children. Toxicity appears acceptable.

Life threatening haemorrhage

The extremely small risk of intracranial haemorrhage (less than 1% in most published series[8–11]) persists throughout the period of profound thrombocytopenia and does not diminish. The presence of severe headache with neurological signs in any patient with a very low platelet count should be treated as an emergency and computed tomography should be performed urgently. Major bleeds need not be fatal. Massive doses of allogenic platelets (20 or more donor units) along with high dose methylprednisolone and intravenous immunoglobulin can be given. Such life threatening haemorrhage is the only indication for platelet infusions in ITP. Simultaneous emergency splenectomy and craniotomy under the same anaesthetic can be carried out. The mortality using such an aggressive approach is under 50% with minimal long term sequelae, but the response with treatment has to be rapid.[13, 24]

Late sequelae

Follow up of an acute episode of ITP for a period of six to 12 months is recommended to ensure that the patient does not have the chronic or relapsing variety. There is no evidence that chronic multisystem autoimmune disease or other pathology is likely to ensue in later life, but mothers who have had ITP in the past can give birth to thrombocytopenic babies even if they themselves no longer have reduced platelet counts. Haematologists and obstetricians need to be aware of this.

We most gratefully acknowledge the advice of Professor J Chessells, Dr P Darbyshire, Dr DIK Evans, Dr J Evans, Dr B Gibson, Dr I Hann, Dr F Hill, Dr D King, Dr MM Reid, and Dr R Stevens during the preparation of this document.

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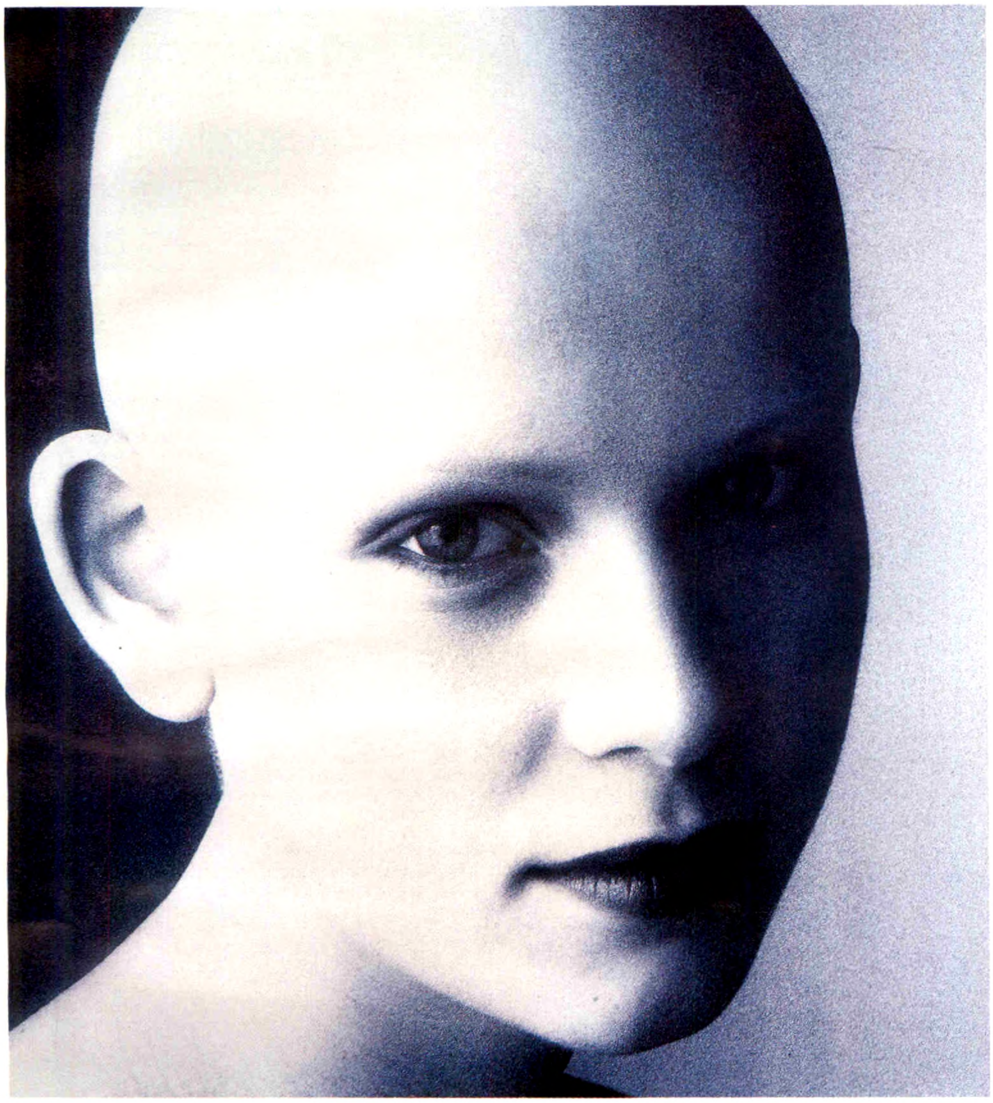

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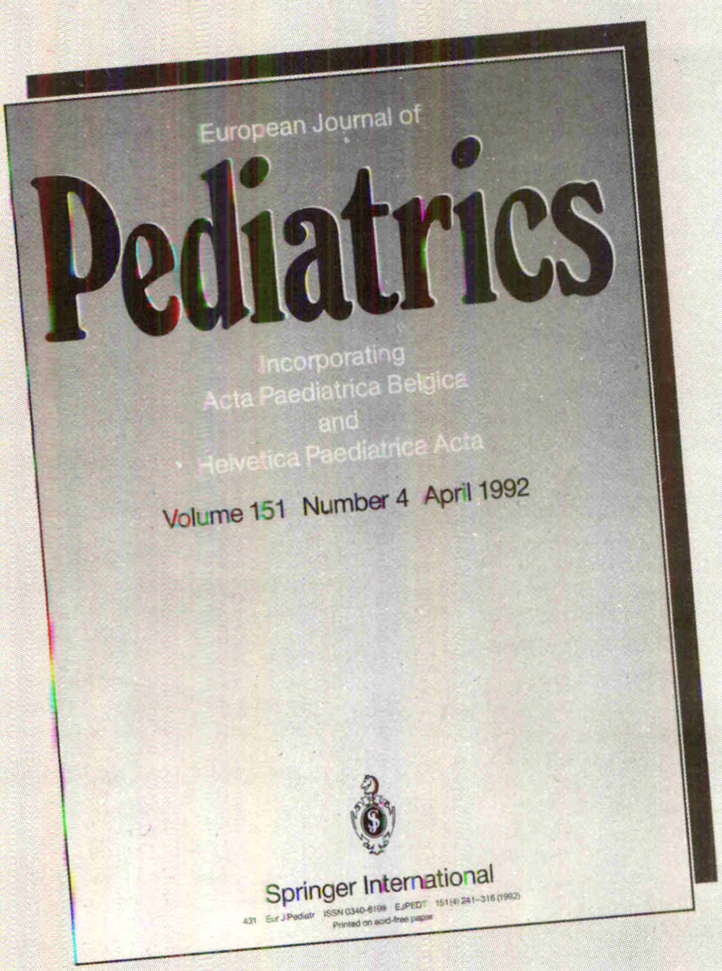

European Journal of

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Volume 151 Number 4 April 1992

Springer International

431 Eur J Pediatr ISSN 0340-6199 EJPEDT 151(4) 241–316 (1992)
Printed on acid-free paper

The **European Journal of Pediatrics** publishes articles from all branches of pediatrics which meet its standards of excellence and authority. It offers a rapid transition time from acceptance to publication.

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LETTERS TO THE EDITOR

Asthma: a follow up statement from an international paediatric asthma consensus group

SIR,—I was surprised to find in this very comprehensive and helpful consensus statement on asthma,[1] no mention about the short course of oral steroids that has in recent years become widely, yet so uncritically, used in the treatment of acute exacerbations of asthma: the use of oral steroids is referred to only in the context of managing severe asthma. Yet most children whom I see in hospital who have been treated with prednisone by the general practitioner at home or in hospital on admission by junior staff have been far from seriously ill. It is so easy for the occasional short course of prednisone to become for some children almost continuous therapy with its well known possible side effects. Can the Steering Committee advise on this?

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1 International Paediatric Asthma Consensus Group. Asthma: a follow up statement from an international paediatric asthma consensus group. *Arch Dis Child* 1992;**67**:240–8.

Professor Warner comments:

Professor Davies expresses a sentiment that I would personally very strongly support. The consensus statement is very clear that in the development of acute exacerbations of asthma, oral steroids are given after it has been established that an optimal dose of inhaled bronchodilators has not been effective or a relapse has occurred within four hours. This is stated in the acute asthma section. However, there is no further elaboration because there was some diversity of opinion about the exact time when oral steroids should be employed.

Professor Davies is correct in stating that uncritical use of oral steroids has resulted in excessive inappropriate use during mild exacerbations. It should, however, be appreciated that asthma deaths have been associated with failure to employ steroids in a severe attack and sometimes the course can be rapid in infancy or not appreciated in older patients.

In the final analysis, it is the interpretation of one or two words in publications on the use of short course oral steroids that dictates whether they are used appropriately or not. Storr *et al* completed a study of a single dose of prednisolone in 140 children 'if their symptoms were moderate or severe on initial assessment'.[1] Unfortunately there is no further elaboration on this point. However, the results very convincingly demonstrated the effects of the treatment in reducing the necessity for hospital admission and for further steroid treatment. I would suggest that moderate or severe asthma means an inadequate response to a nebulised dose of bronchodilator or a relapse of symptoms within four hours of the dose. Employing such criteria should reduce the frequency of steroid usage while ensuring that it is given to those who need it.

1 Storr J, Barrell E, Barry W, Lenney W, Hatcher G. Effect of a single oral dose of prednisolone in acute childhood asthma. *Lancet* 1987;**i**:1879–81.

Axillary and rectal temperature measurements in infants

SIR,—Parents and family doctors commonly measure children's temperatures when they are ill and it is a routine assessment when in hospital. Yet there is uncertainty about where to measure the temperature and what instrument to use. Morley and colleagues from their recently reported observations concluded that a rectal temperature is a more 'precise measurement'.[1] Choosing a site for recording temperature depends not only on its potential precision but also the possibilities of errors and hazards. In 1949 Karlberg found that temperature recorded increased the further the thermometer was inserted into the rectum.[2] In newborn infants Chellappah showed the mean increase between 1 and 2 cm from the anal margin was 0·2°C, and 0·05–0·09°C for every 1 cm beyond this up to 5 cm.[3] If the baby strained during the measurement the temperature increased 0·1°C, a change that persisted for up to 5 minutes with the passage of faeces. Morley and colleagues aimed to measure the temperature 3 cm from the anal margin. However, imprecise placement, which is bound to occur, could easily introduce a difference of 0·5°C.

Although they found no correlation between rectal or axillary temperature and time of day (8 am to 8 pm) other studies have shown an appreciable diurnal variation, where the rectal temperature in a normal healthy baby can vary between 36·0°C and 37·8°C.[4 5] To use a specific temperature to define fever, whether rectal or axillary, is therefore somewhat arbitrary as it will depend on the time of day, the individual, and the activity.

With rectal temperature measurement cross infection hazards and the risk of rectal perforation, small but real,[6] need to be considered. Furthermore as children get older, comfort and the acceptability of rectal thermometry become increasingly relevant. For these reasons we still favour measuring the temperature in the axilla.

The paper from Morley and colleagues serves to remind us of the problems of taking and interpreting body temperature and it would be unfortunate if the temperature, rectal or axillary, were to become the focus of attention rather than taking a history and examining the infant.

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6 Frank JD, Brown S. Thermometers and rectal perforations in the neonate. *Arch Dis Child* 1978;**53**:824–5.

Dr Morley and coauthors comment:

If we take an infant's temperature we should do it as accurately as possible, otherwise the measurement may be misleading, the infant interfered with unnecessarily, and precious time wasted.

We know that rectal temperature is dependent on how far the thermometer is inserted. However, we specifically used the temperatures taken by paediatric nurses. These may not always be accurate but they are the material we work with every day. Temperatures taken as a physiological study may be slightly more accurate but do not represent clinical practice. We found that rectal temperature was higher than axillary in 98% of the pairs of measurements and therefore deduced that it must be closer to the true body temperature.

Whatever the imprecision of rectal temperature measurement, axillary temperatures are more imprecise. Axillary temperatures cannot be used as a proxy for rectal temperature, even by adding a 'fudge' factor, because the difference between them is not constant. In 937 pairs of measurements we found wide differences between them, with axillary temperatures from 0 to 3°C lower. If only axillary temperature is measured there will be a few infants who have a normal axillary temperature even though their rectal temperature is high.

We know that body temperature falls at night after the first few weeks. The range of this has been well documented in infants by Wailoo and Petersen. However, we specifically stated that we recorded daytime temperatures and found no variation during this time. This was a cross sectional study, and individual babies' temperature will vary from hour to hour.

The hazard of perforation of the rectum has been exaggerated. The very few reported cases are all in neonates, some of whom may have had a spontaneous perforation. Considering the millions of times rectal temperatures are taken round the world, the risk must be almost infinitely small. There are no reports of rectal perforation in infants after the neonatal period. Both rectal and axillary thermometers may cause cross infection. This can be prevented by simple sterilisation.

We investigated infants, but those who have studied older children also highlighted the inaccuracy of axillary temperature measurement.[1] We entirely agree that temperature measurement plays only a small part in assessing the severity of a an infant's illness, hence our papers on the importance of symptoms and signs of illness[2] and the development of the Baby Check system.[3] If we are not going to abandon temperature measurement, we are duty bound to measure it as accurately as possible.

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BOOK REVIEWS

Clinical Pediatric Oncology. 4th Ed. By Donald J Fernback and Teresa J Vietti. (Pp 720; £70·50 hardback.) Mosby-Year Book Inc, 1991. ISBN 0–8016–3306–0.

Despite paediatric oncology being one of the most rapidly expanding fields in clinical paediatrics, there are relatively few comprehensive texts. This fourth edition of *Clinical Pediatric Oncology* has been extensively revised and attempts to combine both an up to date review of clinical conditions as well as a basic understanding of the pathology involved.

The book is divided into two main sections. The first section covers the epidemiology and aetiology of childhood malignancy, diagnostic techniques, and general aspects of supportive care. The chapter on imaging in paediatric oncology is superbly illustrated while the chapters on molecular oncology and tumour immunology are both excellent, detailed, if somewhat complex reviews of exciting areas of recent research.

The second section of 16 chapters covers specific disease entities, diagnosis, management, and prognosis. Each is well illustrated with appropriate clinical photographs, *x* ray pictures, and tabulated data which makes each chapter very readable. Finally with significant improvments in survival from childhood malignancies, the last chapter on the late sequelae of cancer and cancer treatment is particularly relevant. It is a concise overview of the many potential problems of the long term survivor and emphasises the necessity for prolonged follow up not only in the patient but of any offspring. As with most chapters it is extensively referenced.

This textbook, though aimed primarily at the paediatric oncologist, would be a valuable reference book for the general paediatrician and those in training. It gives an up to date comprehensive overview of paediatric malignancy from diagnosis to potential problems in the survivor. As with many multiauthor publications there is occasional overlap between chapters, but generally this is minimal.

DENISE M WILLIAMS
Clinical lecturer in paediatrics

Hydrocephalus: Current Clinical Concepts. By R W Leech and R A Brumback. (Pp 212; £46 hardback.) Mosby Year Book, 1991. ISBN 0–8151–5555–7.

The first section of this book is concerned with the basic science of hydrocephalus and deals with the embryological, anatomical, physiological, and pathological aspects in what is quite an elegant synopsis of the scientific background of hydrocephalus. Although not a rigorous bibliography, it is this section wherein lies the strength of the book.

The second half of the book comprises clinical considerations—presentation of hydrocephalus, evaluation, genetic implications, medical and surgical management, and psychosocial factors. While some of these chapters are discussive and useful, others are more flippant and not particularly practical. The paediatrician most frequently encounters practical management difficulties in children with posthaemorrhagic hydrocephalus, or that associated with aqueduct stenosis or Arnold-Chiari malformation and would value assistance in the sometimes thorny problems concerning monitoring progression of ventricular dilatation, the assessment and relationship to brain damage, the indications for cerebrospinal fluid diversion, and later the major problems of blocked, infected, colonised, and overdrained shunts. My main concerns with this book revolved around the question of the 'current clinical concepts' which is purports to deal with, and yet some of the above problems are barely touched on. For example, there is virtually no information on the important use of ultrasound, Doppler indices, pressure and hydrodynamic measurements, but instead one sees dated illustrations such as air encephalograms, which are said to be a deliberate inclusion to illustrate the difficulties of management in the last two to three decades but would be more relevant for an historical text.

While this is an undeniably laudible attempt to compile a book which deals with all aspects of hydrocephalus from the fetus to the geriatric patient with normotensive hydrocephalus, and which is both a reference for specialists and paraprofessionals, and is also of use to families of patients with hydrocephalus, it becomes an almost impossible task in 200 pages and therefore misses the mark in some of its designated aims.

It is always difficult to get authors to address important practical problems which arise in the hinterland between paediatrics, neurosurgery, neurology, and several other 'ologies'. These authors have attempted a very difficult task and this modest book with a largely American faculty has some interesting and useful facets. One must agree with their final comments that 'although we have come a long way the reader must appreciate that there is still much that we do not know about hydrocephalus'.

R A MINNS
Consultant paediatric neurologist

The Epidemiology of Childhood Hyperactivity. By Eric Taylor, Seija Sandberg, Geoffrey Thorley, and Susan Giles. (Pp 148; £27 hardback.) Oxford University Press, 1991. ISBN 0–19–262172–6.

Hyperactivity, the enduring trait of inattentive, restless, and uncontrolled behaviour, is a common complaint by parents of psychiatrically disturbed children. It can feature as a symptom in a number of psychiatric disorders but it also forms the core symptomatology for the hyperkinetic syndrome or attention deficit disorder. There has been considerable discrepancy in rates of hyperkinetic syndrome diagnoses in different countries, reflecting the different emphasis placed on the symptom of hyperactivity as being primary or secondary to other psychiatric difficulty. Because of the suggested links between hyperkinesis and neurodevelopmental anomalies, the diagnosis is used more widely by those clinicians who favour a biological understanding of disruptive behaviour and, because of the response to stimulant medication, by those who use pharmacological treatment.

Drs Taylor, Sandberg, and collaborators at the Institute of Psychiatry have for some years been carrying out research in this area. Previous work by them in clinical samples has shown that it is possible to separate dimensions of hyperactivity from other antisocial or disruptive behaviours, and that a group of children with pervasive hyperactivity and inattention can be recognised, characterised by neurodevelopmental delays and a marked response to stimulant medication, as distinct from groups of children with antisocial behaviour associated with family dysfunction.

The study reported in this book is an epidemiological survey of boys in east London; it examines the generality of the authors' earlier findings. Over 3000 boys were screened using teacher and parent rating scales for disruptive behaviour and its components (hyperactivity and conduct or antisocial behaviour). Subgroups of boys with different types of disruptive behaviour were then selected for detailed study, including the use of standardised measures of child symptomatology, family life, relationships, and social background and a battery of psychological tests. Developmental records were scrutinised for developmental problems. The results confirm and extend the previous findings in clinical samples. A group of hyperkinetic children could be identified from children with non-hyperactive conduct disorders, hyperkinesis being a condition of early onset associated with multiple motor and cognitive developmental delays. They also confirm the existence of a mixed group of children with both hyperactive and conduct disorders and they show a tendency for hyperactive children to have more symptoms of emotional disorder than other children.

The work was conducted carefully; the methodology is sound, the analysis thorough and discriminating. The discussion is an authoritative outline of the state of the art as regards research on the basic features of the syndrome and its associations. I found the discussion on why laboratory studies of attention appear to be out of keeping with clinically observed hyperkinetic or overactive behaviour particularly interesting. The book is required reading for anyone wanting to have a sophisticated and scientifically discriminating approach to the nature of the hyperkinetic syndrome.

M E GARRALDA
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